IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMERICAN ACADEMY OF HIV MEDICINE; HIV MEDICINE ASSOCIATION, a division of the INFECTIOUS DISEASES SOCIETY OF AMERICA; INTERNATIONAL ASSOCIATION OF PROVIDERS OF AIDS CARE; JENNIFER K. BRODY, MD; and CHRISTOPHER B. FOX, NP, *Plaintiffs*, v. HEALTH RESOURCES AND SERVICES ADMINISTRATION; THOMAS J. ENGELS, in his official capacity as the Administrator of the Health Resources and Services Administration; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; and ROBERT F. KENNEDY, JR., in his official capacity as Secretary of the U.S. Department of Health and Human Services, *Defendants*.	Case No.

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION

1. LGBTQ[1] people, and particularly transgender people, have faced a long history of hostility, neglect, bigotry, and erasure by the institutions charged with safeguarding their health. This includes the HIV/AIDS crisis, when an untold and disproportionate number of gay men and transgender women, particularly people of color, suffered and died as their government looked the other way.

[1] LGBTQ refers to lesbian, gay, bisexual, transgender, and queer people. Throughout this Complaint, Plaintiffs use "LGBTQ" as an umbrella term to be read as inclusive of all people with these sexual or gender identities.

2. Since 1981, when AIDS was first discovered, LGBTQ people have been disproportionately affected by the HIV/AIDS epidemic. So much so that even though HIV may be acquired by anyone, some considered HIV/AIDS to be a "gay plague."

3. By the late 1980's, the HIV/AIDS epidemic had created a need for primary medical care that exceeded the capacity of local health departments, hospital emergency rooms, and other healthcare providers. People living with HIV were struggling to obtain desperately needed medical care.

4. The federal government began to respond to the HIV/AIDS epidemic, after much delay, toward the end of the 1980s and early 1990s. In 1990, for example, Congress created the Ryan White HIV/AIDS Program ("the Ryan White Program" or "the Program").

5. Since its inception, the Ryan White Program, which is administered by the Health Resources and Services Administration ("HRSA"), has helped states, communities, and people living with HIV cope with the impact of the HIV/AIDS epidemic. The Program supports systems of care for people living with HIV who do not have adequate health insurance or sufficient financial resources to access the care they need, tailoring programs based on local needs and resources. The Program is founded on strong partnerships between the federal government, states, and local communities in need. The Program emphasizes and facilitates access to outpatient, primary care to improve overall health outcomes and minimize costly emergency room visits and hospitalizations.

6. Congress directed that funding under the Ryan White Program be targeted to historically underserved communities and populations, and that patients in need receive comprehensive medical and mental healthcare to assure the best overall health outcomes, including compliance with HIV treatment. This approach has been a resounding public health success.

Among other things, it has helped to achieve rates of viral suppression in the population served by the Ryan White Program that far exceed that of the general population of patients living with HIV. This, in turn, has helped contain the spread of HIV/AIDS in the larger population.

7. Transgender people living with HIV have particularly benefited from access to HIV care and comprehensive primary care through the Ryan White Program. Thousands of transgender people living with HIV have long relied on Ryan White-funded clinics and medical practices for their HIV care and their overall health needs. Defendants have long recognized—and reaffirmed as recently as 2024—that affirming healthcare (i.e., care that is mindful and respectful of a transgender patient's identity) and medical treatment for gender dysphoria (including gender-affirming hormone therapy) are a necessary part of providing comprehensive care to transgender patients with HIV. Affirming healthcare and medical treatment for gender dysphoria (known as "gender-affirming medical care") are also crucial to encouraging such patients to enter and stay in treatment for HIV, increasing adherence to antiretroviral therapy ("ART"), and viral suppression. And healthcare providers have relied on the government's long-time understanding that Ryan White funds can and should be used to address the comprehensive primary health needs of patients with HIV, including the treatment of co-occurring conditions, to build integrated care models that provide holistic care to all patients living with HIV, including transgender patients.

8. Yet, notwithstanding HIV's disproportionate impact on transgender people and the historical success of the Ryan White Program in achieving viral suppression in this population, Defendants have sought to restrict transgender people's access to HIV care through the Ryan White Program. Defendants have adopted a policy that HRSA funding recipients may not acknowledge, affirm, or respect the identities of transgender people, and may not use federal funding in a way that promotes so-called "gender ideology," including through the provision of gender-affirming

medical care. This is just one piece of the Trump administration's broad campaign to erase the identities of transgender people and limit their ability to participate in public life, including by limiting access to the medical care some transgender people need to live authentically as themselves.

9. Defendants have recently sought to operationalize the administration's discriminatory directives by adopting a new set of "FY2026 HRSA General Terms and Conditions," issued on March 11, 2026, as well as by issuing Ryan White Program Notices of Funding Opportunities, like the ones pertaining to Ryan White Part B Supplemental, Ryan White Part C, and Ryan White Part F, issued on June 8, 2026. These are the "Challenged Conditions" at issue in this case.

10. These discriminatory directives have caused confusion, fear, and concern among HIV care providers and transgender patients living with HIV who rely on Ryan White funding. If implemented, the Challenged Conditions would require HIV care providers to refuse to acknowledge, affirm, or respect the identities of their transgender patients and would forbid these providers from using Ryan White funding to provide transgender patients with gender-affirming hormone therapy—even though the Ryan White Statute explicitly contemplates such care as an outpatient service provided as part of a patient's primary care. These actions, in turn, risk exacerbating the HIV epidemic by making it less likely that transgender patients will engage with HIV care, reducing adherence to HIV treatment regimens, and increasing the likelihood of HIV transmission in the broader community.

11. Defendants' actions are not just unconscionable; they are unlawful. They flaunt the text, purpose, and structure of the Ryan White statute as well as statutory and constitutional guarantees against discrimination.

12. Plaintiffs are HIV care providers and associations whose members are HIV care providers. They bring this case to prevent the devastating consequences of Defendants' actions from occurring. In doing so, they assert multiple claims.

13. Under the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701-706, federal agencies—including the U.S. Department of Health and Human Services ("HHS") and HRSA—must act rationally, transparently, and in accordance with the law. Defendants have done the opposite here.

14. Additionally, Defendants' conduct runs afoul of Section 1557 of the Affordable Care Act ("ACA"), 42 U.S.C. § 18116, which prohibits discrimination based on sex in federally funded health programs, including in HIV care programs administered or funded by HHS and HRSA.

15. Beyond their statutory infirmities, Defendants' actions violate core constitutional protections. The Fifth Amendment's guarantee of equal protection bars the federal government from targeting a group for disfavored treatment, including based on sex and transgender status, which is precisely what Defendants are attempting to do here. The First Amendment, in turn, is violated because the government unlawfully seeks to leverage funding to regulate speech outside the contours of the program itself and threatens to withhold benefits for a censorious purpose.

16. Because the federal government cannot pick and choose whose health matters based on politics or prejudice, and to prevent irreparable harm to HIV care providers and their transgender patients, Plaintiffs seek injunctive relief to stop Defendants from enforcing or implementing the discriminatory policies at issue and to stop and set aside the incorporation and implementation of said policies within Ryan White funding streams. Preliminary injunctive relief

is necessary to preserve the status quo while this Court evaluates the legality of Defendants' actions.

17. The stakes could not be higher. At its core, this lawsuit is about whether the federal government may single out an already marginalized group for exclusion from the nation's public health agenda. Under our Constitution and laws, the answer must be no.

JURISDICTION AND VENUE

18. This Court has jurisdiction pursuant to 28 U.S.C. § 1331, as this action arises under the laws of the United States and the United States Constitution; 28 U.S.C. § 1346, as a civil action against the United States founded upon the Constitution, an Act of Congress, or an executive regulation; and 28 U.S.C. § 1361, as an action to compel an officer or agency to perform a duty owed to plaintiffs.

19. Jurisdiction also is proper under the Administrative Procedure Act, 5 U.S.C. §§ 701-706.

20. An actual controversy exists between the parties within the meaning of 28 U.S.C. § 2201(a), and this Court may grant declaratory, injunctive, and other relief pursuant to 28 U.S.C. §§ 2201-2202 and 5 U.S.C. §§ 705-706.

21. Venue is proper in this district pursuant to 28 U.S.C. § 1391(b)(2), (c)(2), and (e)(1). Plaintiff Dr. Jennifer K. Brody is a resident of this district who resides in Boston, Massachusetts, as are members of Associational Plaintiffs. Each defendant is an agency of the United States or an officer of the United States sued in their official capacity, and Defendant HRSA maintains an office in Boston, Massachusetts. A substantial part of the events or omissions giving rise to this Complaint occurred and continue to occur within the District of Massachusetts.

PARTIES

A. Plaintiffs

22. Plaintiff **American Academy of HIV Medicine (the "Academy")** is a nonprofit membership organization based in Washington, DC. It is the leading independent organization of healthcare professionals dedicated to providing excellence in HIV care and prevention. The Academy's mission is to ensure healthcare professionals have the resources needed to prevent, treat, and care for those with or at risk for HIV and related conditions to achieve optimal health.

23. The Academy's membership of HIV practitioners and credentialed providers, which together amount to over 5,000 providers, give direct care to the majority of patients living with HIV in the United States.

24. Academy members rely on the Ryan White Program to provide comprehensive healthcare to patients living with HIV, including transgender patients. Almost half of the Academy's members rely on funding under the Ryan White Program to provide gender-affirming medical care to their patients living with HIV.

25. Among the members of the Academy whose practices and patients stand to be impacted by the Challenged Conditions are Plaintiffs Dr. Jennifer K. Brody and Nurse Practitioner Christopher B. Fox, as well as Dr. Michelle Collins-Ogle, who is based in North Carolina, and Nurse Practitioner Danielle Doe, who is based in Massachusetts.

26. Academy members rely on all parts of the Ryan White Program to provide health services and care for their patients living with HIV, including transgender patients. This includes Plaintiff Brody and her patients who benefit from Parts A, B, and C; Plaintiff Fox and his patients who benefit from Parts A, B, and F; Dr. Collins-Ogle and her patients who benefit from Parts B, B Supplemental, and C; and NP Doe and her patients who benefit from Parts B, C, D, and F.

27. Plaintiff **HIV Medicine Association ("HIVMA")**, a division of the **Infectious Diseases Society of America ("IDSA")**, is an organizational component of IDSA comprising nearly 6,000-member healthcare professionals who advance a comprehensive and humane response to the HIV pandemic, informed by science and social justice. IDSA is based in Arlington, Virginia, and is a national professional medical society representing 13,000 physicians, scientists, and other health professionals who specialize in infectious diseases.

28. HIVMA works to increase access to healthcare services and coverage for people living with HIV and populations heavily impacted by HIV and to foster a robust, diverse, and culturally competent HIV workforce.

29. HIVMA members have led the Ryan White Medical Providers Coalition ("the Coalition") for more than twenty years. The Coalition comprises HIV clinicians and is a leading voice in federal advocacy related to Ryan White HIV/AIDS Program funding and policies. Many HIVMA members provide gender-affirming medical care to their patients living with HIV in accordance with well-established clinical guidelines, like HIVMA's own *Primary Care Guidance for Providers Who Care for Persons with Human Immunodeficiency Virus*.

30. Among the members of HIVMA whose practices and patients stand to be impacted by the Challenged Conditions are Plaintiff Dr. Brody, as well as members Dr. Collins-Ogle and Dr. Rachel Roe, who is based in Tennessee.

31. HIVMA members rely on all parts of the Ryan White Program to provide health services and care for their patients living with HIV, including transgender patients. This includes Plaintiff Brody and her patients who benefit from Ryan White Parts A, B, and C; Dr. Collins-Ogle and her patients who benefit from Parts B, B Supplemental, and C; and Dr. Roe and her patients who benefit from Parts A, B, B Supplemental, C, D, and F.

32. Plaintiff **International Association of Providers of AIDS Care ("IAPAC")** is a nonprofit membership organization based in Washington, DC. It was founded more than four decades ago with a mission to improve access to and the quality of prevention, care, treatment, and support services delivered to people living with and affected by HIV and comorbid diseases, including tuberculosis and viral hepatitis. With more than 30,000 members globally, including in the United States, and programming in more than 150 countries, IAPAC is the largest association of clinicians and allied health professionals working to end AIDS as a public health threat by 2030.

33. IAPAC members rely on funding under the Ryan White Program to provide comprehensive healthcare to patients living with HIV, including transgender patients. Many IAPAC members use Ryan White funding to provide gender-affirming medical care to their patients living with HIV.

34. Among the members of IAPAC whose practices and patients stand to be impacted by the Challenged Conditions is Plaintiff Dr. Brody as well as member Dr. Collins-Ogle.

35. IAPAC members rely on all parts of the Ryan White Program to provide health services and care for their patients living with HIV, including transgender patients. This includes Plaintiff Dr. Brody and her patients who benefit from Parts A, B, and C, and Dr. Collins-Ogle and her patients who benefit from Parts B, B Supplemental, and C.

36. Plaintiff **Jennifer K. Brody, MD, MPH** is a primary care physician based in Boston, Massachusetts. She is affiliated with the Boston Health Care for the Homeless Program (BHCHP). She specializes in addiction medicine, HIV/AIDS treatment, and internal medicine, and serves as the Director of BHCHP's HIV Program. She is board-certified in Internal Medicine and Addiction Medicine by the American Board of Internal Medicine and is a certified HIV Specialist

through the American Academy of HIV Medicine. Dr. Brody is a member of the American Academy of HIV Medicine, HIVMA, and IAPAC.

37. Dr. Brody and her patients benefit from funding under Parts A, B, and C of the Ryan White Program, which supports the integrated delivery of medical care, medications, and critical support services for low-income individuals living with HIV. In her clinical practice, Dr. Brody provides gender-affirming medical care, including hormone therapy, as part of comprehensive HIV treatment to HIV positive transgender patients.

38. Plaintiff **Christopher B. Fox, NP** is a nurse practitioner specializing in HIV care and prevention and an Assistant Professor of Medicine in the Division of Internal Medicine and Geriatrics at Oregon Health & Science University ("OHSU") in Portland, Oregon. At OHSU, he delivers HIV primary care to approximately 300 patients, consults on HIV management, and leads an OHSU telehealth Program. NP Fox has written chapters in Collins-Bride & Saxe's Clinical Guidelines textbook on *Advanced Practice Nursing: HIV Infection in Adolescents and Adults* and *Primary Care of HIV-Infected Adults*. NP Fox is a member of the American Academy of HIV Medicine and is a certified HIV Specialist through the American Academy of HIV Medicine.

39. NP Fox and his patients benefit from funding under Parts A, B, and F of the Ryan White Program. NP Fox is the primary care provider for the majority of his transgender patients living with HIV. He provides gender-affirming medical care as part of his patients' primary care.

40. Plaintiffs **Dr. Brody** and **NP Fox** are collectively referred to as the **Provider Plaintiffs**. Provider Plaintiffs assert claims on behalf of themselves and on behalf of their transgender patients living with HIV who rely on the Ryan White Program for their medical care.

41. Plaintiffs **The Academy**, **HIVMA**, and **IAPAC** are collectively referred to as the **Associational Plaintiffs**. Associational Plaintiffs assert claims on behalf of their members who

receive Ryan White funding and on behalf of their members' transgender patients living with HIV who rely on the Ryan White Program for their medical care.

B. Defendants

42. Defendant **Health Resources and Services Administration ("HRSA")**, an agency of the U.S. Department of Health and Human Services, is the primary federal agency responsible for improving access to healthcare for people who are uninsured, geographically isolated, or medically vulnerable. Through its HIV/AIDS Bureau, HRSA administers the Ryan White Program. HRSA is an "agency" within the meaning of the APA. 5 U.S.C. § 551(1). HRSA is headquartered in Washington, DC, and it maintains an office in Boston, Massachusetts.

43. Defendant **Thomas J. Engels** is the Administrator of the HRSA. He is sued in his official capacity. As HRSA Administrator, he is responsible for setting policy for HRSA and for planning, managing, and coordinating the programs and activities of all HRSA bureaus and offices.

44. Defendant **U.S. Department of Health and Human Services ("HHS")** is an executive cabinet department of the United States government. It houses and oversees HRSA. HHS is responsible for the administration of federal health programs, including the Ryan White Program. HHS is an "agency" within the meaning of the APA. 5 U.S.C. § 551(1). HHS is headquartered in Washington, DC.

45. Defendant **Robert F. Kennedy, Jr.** is the Secretary of HHS. He is sued in his official capacity. As Secretary, he is responsible for all aspects of the operation and management of HHS, including all its programs, operating divisions, and activities, as well as for implementing HHS's duties under federal law.

FACTUAL BACKGROUND AND ALLEGATIONS

I. LGBTQ People and HIV

46. The Human Immunodeficiency Virus ("HIV") epidemic emerged in the early 1980's as a devastating and poorly understood public health crisis. At the outset, many young and otherwise healthy people became ill with a wide array of rare and often deadly infections, later identified as Acquired Immunodeficiency Syndrome ("AIDS").

47. AIDS was initially perceived not as a national health problem but as a problem for "homosexuals" and intravenous drug users.

48. In the early years of the HIV epidemic, the federal government's response was marked by delay and inaction, even as thousands of people—disproportionately gay men, transgender women, and people of color—were dying.[2] As a 2011 report by the Institute of Medicine (now the National Academy of Medicine) documents, "Because of the marginal status of these groups, societal response to the epidemic was slow."[3]

49. In response to this vacuum, grassroots activists mobilized to demand urgent governmental action, challenge stigma, and advocate for access to lifesaving treatment and research. These advocacy efforts fundamentally reshaped the national response to HIV and laid the groundwork for a more robust federal role.

50. Still, as the 2011 Institute of Medicine report documents, "It was not until there was widespread awareness that AIDS was affecting the 'mainstream' population that the disease

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[2] Theodore J. Padamsee, *Fighting an Epidemic in Political Context: Thirty-Five Years of HIV/AIDS Policy Making in the United States*, 33 Soc. Hist. Med. 1001, 1003–05 (2020).

[3] Institute of Medicine, *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding* 68, (2011).

garnered significant attention. Indeed, it was Ryan White, an Indiana adolescent who contracted AIDS through treatment for hemophilia, who became the sympathetic face of AIDS to the nation."[4]

51. Against this backdrop of sustained community advocacy and mounting public pressure, Congress enacted the Ryan White Comprehensive AIDS Resources Emergency Act of 1990 to establish a national system of care for individuals living with HIV, particularly those with limited financial resources.[5] Though the Act was named after the young cisgender straight white teenager who captured the nation's attention, the statute nonetheless reflected a deliberate shift from indifference toward a comprehensive, equity-driven public health response designed to improve access to care, promote retention in treatment, and address the structural barriers that had previously left marginalized populations without adequate medical and support services.[6]

A. HIV Disproportionately Affects LGBTQ People and Communities of Color.

52. Although HIV affects people across the United States, the epidemic continues to fall disproportionately on LGBTQ people and communities of color.[7]

53. In the latest publicly compiled national data, lesbians, gay men, and bisexual individuals accounted for 67% of the estimated 31,800 new HIV infections in 2022.[8] Black people comprised approximately 12% of the U.S. population but accounted for 37% of estimated new HIV infections, while Hispanic or Latino people comprised approximately 18% of the population but accounted for 33% of new infections.[9] The Centers for Disease Control and Prevention

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4 *Id.*

5 Institute of Medicine, *Public Financing and Delivery of HIV/AIDS Care: Securing the Legacy of Ryan White* 37–39, (2005).

6 The White House, *National HIV/AIDS Strategy for the United States 2022–2025* 6–8 (2021), https://tinyurl.com/4ab8rv2d [https://perma.cc/2GH5-JJV8].

7 HIV.gov, *U.S. Statistics* (Feb. 25, 2026), https://tinyurl.com/3dzufnk5 [https://perma.cc/5TKH-E4GK]

8 *Id.*

9 *Id.*

("CDC") reports that in 2023 Black and Hispanic or Latino individuals each accounted for more than one-third of new HIV diagnoses nationwide, far exceeding their proportionate share of the general population.[10]

54. Within the broader HIV epidemic, transgender individuals, particularly transgender women, experience some of the highest rates of HIV prevalence in the country and the most significant barriers to care.

55. The CDC estimates that approximately 14% of transgender women in the United States are living with HIV, a rate far exceeding that of the overall population.[11] HIV prevalence among transgender women is more than 34 times higher than among other adults of reproductive age.[12] In another CDC study of transgender women in major U.S. cities, approximately 42% tested positive for HIV, with even higher rates among Black transgender women.[13]

56. The burden of HIV among transgender women is compounded by stark racial disparities. Black transgender women account for a disproportionate share of HIV diagnoses, representing approximately 44% of diagnoses among transgender women, followed by Hispanic/Latina transgender women at 26%.[14] These disparities mirror broader patterns of racial inequity in the HIV epidemic while illustrating their particularly acute impact within transgender communities.

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[10] Centers for Disease Control & Prevention, *HIV Diagnoses, Deaths, and Prevalence: 2025 Update* (Apr. 29, 2025), https://tinyurl.com/5n85xfmf [https://perma.cc/U9CT-JR66]

[11] Centers for Disease Control & Prevention, *Sexually Transmitted Infections Treatment Guidelines: 2021, Transgender and Gender Diverse Persons* (2021), https://tinyurl.com/jcjskthp [https://perma.cc/PLX2-H25M].

[12] Marc A. Pitasi et al., *HIV Testing and Linkage to Care Among Transgender Women Who Have Sex with Men: 23 U.S. Cities*, 24 AIDS Behav. 2442 (2020), https://tinyurl.com/bde7f5yb [https://perma.cc/RDF5-3MNR].

[13] Centers for Disease Control & Prevention, *HIV Infection Among Transgender Women — Seven U.S. Cities, 2019–2020*, 71 Morbidity & Mortality Wkly. Rep. 1 (2022); see also American Hospital Association, CDC Reports 42% HIV Rate in Transgender Women Surveyed in 7 Cities (Apr. 19, 2021), https://tinyurl.com/4bahvssk [https://perma.cc/L5FP-SVVC].

[14] Centers for Disease Control & Prevention, *Sexually Transmitted Infections Treatment Guidelines: 2021 Transgender and Gender Diverse Persons* (2021), https://tinyurl.com/jcjskthp [https://perma.cc/PLX2-H25M].

57. This disproportionate impact is driven not by individual behavior alone, but by well-documented structural and social determinants of health. Federal public health authorities recognize that stigma, discrimination, poverty, homelessness, and limited access to culturally competent healthcare significantly increase HIV risk among transgender women.[15] Empirical studies confirm that these factors – including housing instability, lack of insurance, and barriers to gender-affirming medical care – are strongly associated with increased HIV incidence. As a result, transgender women face heightened exposure to HIV alongside diminished access to the very services designed to prevent and treat it.[16]

II. The Ryan White Program

58. The Ryan White HIV/AIDS Program ("the Ryan White Program") is the largest federal program dedicated to HIV care and treatment. Congress enacted the Ryan White Comprehensive AIDS Resources Emergency Act (hereafter, the "Ryan White CARE Act" or the "Ryan White statute"), codified as amended at 42 U.S.C. §§ 300ff–11 to 300ff–140, in 1990 to provide a complete system of care for low-income individuals living with HIV who lack sufficient health coverage or financial resources.[17] The statute was amended and reauthorized in 1996, 2000, 2006, and 2009.

59. Congress created the Ryan White Program expressly to meet the *comprehensive* health-related needs of those living with HIV. The statute's central purpose is to "improve the

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[15] Centers for Disease Control & Prevention, *HIV, Fast Facts: HIV and Transgender People* (Mar. 28, 2024), https://tinyurl.com/mvd7bduh [https://perma.cc/HW73-GHW8].

[16] Elana Morris et al., *Characteristics Associated with Pre-Exposure Prophylaxis Discussion and Use Among Transgender Women Without HIV Infection —National HIV Behavioral Surveillance Among Transgender Women, Seven Urban Areas, United States, 2019–2020*, 73 Morbidity & Mortality Wkly. Rep. (Supp. 2024), https://tinyurl.com/27xmstnc [https://tinyurl.com/27xmstnc].

[17] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., HIV/AIDS Bureau, Policy Clarification Notice 21-02, *Determining Client Eligibility & Payor of Last Resort in the Ryan White HIV/AIDS Program* (Oct. 19, 2021), https://tinyurl.com/32ad2yjv [https://perma.cc/HY9G-WJJ7].

quality, availability and organization of health care and support services for individuals and families with HIV/AIDS" who are low-income and lack the resources to otherwise obtain care. 42 U.S.C. § 300ff–21. Thus, the Ryan White Program functions as a payer of last resort by providing care to those with HIV who cannot otherwise access it.

60. The Ryan White statute embodies a broad mandate to provide not only HIV care, but also healthcare services beyond those specifically related to HIV/AIDS treatment, including core medical services, such as outpatient services to treat co-occurring conditions, and support services for people living with HIV. Congress reiterated that broad mandate when it reauthorized the Ryan White Program in 2006, explaining that the statute's purpose "is to address the unmet care and treatment needs of persons living with HIV/AIDS by funding primary health care and support services that enhance access to and retention in care." H.R. Rep. No. 109-695, at 2 (2006).

61. Congress also understood that States and local governments are best positioned to identify the particular needs of their communities. Congress therefore structured the Ryan White Program to provide funding to States and local jurisdictions, which in turn determine how to allocate the funds to the providers in their communities through a system of local planning councils and healthcare consortia that are tasked with determining the needs of the local population living with HIV/AIDS. *See Ryan White Care Act Amendments of 2000*, 146 Cong. Rec. S10029-02, S10030 (2000) ("The bill remains primarily a system of grants to State and local jurisdictions, thereby ensuring that grantees can respond to local needs. States, EMAs [Eligible Metropolitan Areas], and the affected communities will still decide how to best prioritize and address the healthcare needs of their HIV-positive citizens. This bill reinforces the ability of States and [Eligible Metropolitan Areas] to identify and meet local needs."). Thus, the Ryan White Program

allows the States and local jurisdictions to determine how to serve the needs of persons living with HIV.

62. The Ryan White Program has been a resounding success and is viewed as one of the most successful public health programs in the United States. It is estimated that Ryan White serves more than 600,000 people annually, which is more than half of all people diagnosed with HIV in the United States.[18] And 91.4% of patients who receive care under Ryan White achieve viral suppression, which is significantly better than the national average of 67.2%.[19]

A. The Structure of the Ryan White Program

63. The statutory framework of the Ryan White Program reflects a comprehensive, public health-oriented approach to HIV care that integrates medical treatment, medications, and supportive services necessary to achieve optimal health outcomes. *See* 42 U.S.C. §§ 300ff–14(b)–(d), 300ff–26(a), 300ff–51(b). The statute is organized into multiple Parts, each addressing different components of the national HIV care system. *See generally* 42 U.S.C. §§ 300ff–11 to 300ff–140. Together, the Program establishes a coordinated system of care designed to provide a continuum of HIV services—from diagnosis to treatment to long-term disease management—and other medical care aimed at providing comprehensive care to people living with HIV. *See*, *e.g.*, 42 U.S.C. §§ 300ff–11, 300ff–21, 300ff–51.

64. Part A provides grants to Eligible Metropolitan Areas ("EMAs") and Transitional Grant Areas ("TGAs"). 42 U.S.C. § 300ff–11(a), (b). Part B provides grants to States and Territories. 42 U.S.C. § 300ff–21(a). Part C provides Early Intervention Services grants to public and nonprofit entities to support early intervention services and outpatient care for individuals with

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[18] Health Res. & Servs. Admin, U.S. Dep't of Health & Hum. Servs., Ryan White HIV/AIDS Program Annual Data Report: Ryan White HIV/AIDS Program Services Report 2024 (Dec. 2025), at 1, https://tinyurl.com/57d96udt [https://perma.cc/69XX-63FF].

[19] *Id.* at 2.

HIV. 42 U.S.C. § 300ff–51(a). Part D provides grants for family-centered care for women, infants, children, and youth living with HIV. 42 U.S.C. § 300ff–71(a). And Part F authorizes a range of demonstration and training programs, including initiatives to improve HIV care delivery and workforce capacity. 42 U.S.C. § 300ff–100, 300ff–111, 300ff–121.

65. Part A provides funding to EMAs and TGAs—cities and other local jurisdictions—that are disproportionately affected by HIV. 42 U.S.C. § 300ff–11(a), (b).

66. To allocate Part A funds, the statute establishes HIV health services planning councils made up of healthcare providers, community-based organizations, social service providers, and others. 42 U.S.C. § 300ff–12(b). Those councils are authorized to determine the needs of the local population living with HIV, paying "particular attention to . . . subpopulations and historically underserved communities." *Id. See also Ryan White Care Act Amendments of 2000*, 146 Cong. Rec. S10029-02, S10030 (2000) (stating that underserved communities include rural communities and women, youth, and minorities). Councils are empowered to establish priorities for the allocation of funds, develop a comprehensive plan for the organization and delivery of health and support services, and assess the effectiveness of the services provided.

67. Part B provides formula grants to States and Territories to improve the quality, availability, and organization of HIV healthcare and support services for individuals and families with HIV/AIDS. 42 U.S.C. § 300ff–21. The statute requires States' HIV Consortia to use awarded grants to ensure access to care for low-income individuals and those with limited or no access to health insurance coverage. 42 U.S.C. § 300ff–27(b)(7)(b).

68. Similar to Part A's planning councils, under Part B, States must establish HIV Consortia consisting of healthcare providers, community organizations, and others, with the same responsibilities and priority-setting powers. 42 U.S.C. § 300ff–23.

69. As with Part A, Part B also requires that Consortia assess the needs in their community, develop a comprehensive plan for the organization and delivery of health and support services, assess the effectiveness of the services provided, and prioritize essential health services. *See* 42 U.S.C. § 300ff–23(a), (c).

70. States and Consortia must provide assurances that Part B funds will be used to address disparities in access and outcomes, including among disproportionately affected populations. 42 U.S.C. § 300ff–23(b)(1), 300ff–27(b)(3), 300ff–27(b)(5).

71. Part B also established the AIDS Drug Assistance Program ("ADAP"), which provides access to HIV medications and related treatments. 42 U.S.C. § 300ff–26(a). ADAP funds must be used to provide FDA-approved HIV-related medications and, where applicable, treatments for opportunistic infections. 42 U.S.C. § 300ff–26.

72. Part C provides grants directly to public and nonprofit entities to support early intervention services – such as testing, referrals, and medical evaluations – for individuals living with HIV. 42 U.S.C. § 300ff–51.

73. The purpose of Part C is to support outpatient and ambulatory health services that facilitate early diagnosis, entry into care, and ongoing treatment. 42 U.S.C. § 300ff–51.

74. Part C providers must target individuals who are underserved or at risk of not receiving appropriate HIV care, including those facing structural barriers to treatment. 42 U.S.C. § 300ff–52(a)(1).

75. Funds under Parts A, B, and C must be used to provide "core medical services" and "support services" for individuals living with HIV. 42 U.S.C. §§ 300ff–14(a), 300ff–22, 300ff–51.

76. "Core medical services" encompass a broad array of services and are not limited to specific HIV treatment. They include outpatient and ambulatory health services, ADAP treatments,

oral healthcare, medical nutrition therapy, mental health services, substance abuse outpatient care, and other services. 42 U.S.C. § 300ff–14(c)(3), 300ff–22(b), 300ff–51(c). The statute requires that not less than 75% of Part A funds be used for "core medical services," unless a waiver is granted. 42 U.S.C. § 300ff–14(c)(1).

77. "Support services" are broadly defined as services "that are needed for individuals with HIV/AIDS to achieve their medical outcomes." 42 U.S.C. § 300ff–14(d), 300ff–22(c), 300ff-51(d). The statute lists several examples of those services, including "respite care for persons caring for individuals with HIV/AIDS, outreach services, medical transportation, linguistic services, and referrals for health care and support services." 42 U.S.C. § 300ff–14(d)

78. Part D provides funding for public and nonprofit private entities to provide "family-centered care involving outpatient or ambulatory care . . . for women, infants, children, and youth with HIV/AIDS." 42 U.S.C. § 300ff–71(a).

79. Funding awarded under Part D may be used for a variety of services, including case management, referrals for social and support services, and "additional services necessary to enable the patient and the family to participate in the program established by the applicant pursuant to such subsection including services designed to recruit and retain youth with HIV." 42 U.S.C. § 300ff–71(b).

80. Part F provides funding for several types of projects: special projects of national significance that "quickly respond to emerging needs of individuals receiving assistance," 42 U.S.C. § 300ff–101; projects to further educate healthcare providers about HIV/AIDS prevention and treatment, 42 U.S.C. § 300ff–111; and initiatives such as the Minority AIDS Initiative aimed at addressing "the disproportionate impact of HIV/AIDS on, and the disparities in access, treatment, care, and outcomes for, racial and ethnic minorities," 42 U.S.C. § 300ff–121.

B. Gender-Affirming Medical Care and the Ryan White Program

i. Gender-Affirming Medical Care

81. Many transgender people experience distress as a result of the incongruence between a person's gender identity and their birth-assigned sex. Gender dysphoria is a medical condition marked by the clinically significant distress arising from the incongruence between a person's gender identity and their birth-assigned sex.

82. The American Psychiatric Association codifies gender dysphoria as a diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision* (DSM-5-TR).[20] Gender dysphoria is also recognized as a clinical diagnosis globally, including by the World Health Organization.[21]

83. Medical treatment for gender dysphoria aims to reduce, or even eliminate, the clinically significant distress associated with gender dysphoria by aligning a transgender person's body with their gender identity and thus allowing them to live in a manner consistent with such identity. This treatment is often referred to as "gender-affirming medical care."

84. Healthcare providers who provide gender-affirming medical care, including those who participate in the Ryan White Program, "are informed by expert evidence-based guidelines."[22] These guidelines provide a framework for the safe and effective treatment of gender dysphoria.

85. For example, the World Professional Association for Transgender Health and the Endocrine Society have published widely accepted guidelines for treating gender dysphoria.[23]

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[20] Am. Psychiatric Ass'n, *Diagnostic and Statistical Manual of Mental Disorders* 511 (5th ed., Text Rev. 2022).

[21] World Health Org., *Gender Incongruence*, International Classification of Disease (11th rev. 2018).

[22] Nat'l Acad. Scis., Eng'g & Med., *Understanding the Well-Being of LGBTQI+ Populations* 361 (Patterson, Sepúlveda & White eds., 2020).

[23] Eli Coleman et al., *Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8, 23 Int'l J. Transgender Health S1 (2022); Wylie C. Hembree et al., *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline*, 102 J. Clinical Endocrinology & Metabolism 3869 (2017); *see also* Univ. of Cal., San Francisco, Gender Affirming Health Program, *Guidelines for the Primary*

86. In the context of HIV care, this also includes guidelines like those published by Associational Plaintiffs,[24] as well as those issued by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents, which prior to 2025, including the September 2024 version, contained a section titled "Transgender People with HIV."[25]

87. Under these guidelines, it may be medically necessary and appropriate to treat transgender people experiencing gender dysphoria with gender-affirming hormone therapy, which typically includes prescribing testosterone for transgender men and estrogen and testosterone suppression for transgender women.

88. Medical treatment recommended for and provided to transgender people with gender dysphoria is effective. Gender-affirming medical care can substantially reduce lifelong gender dysphoria. And transgender people's mental health outcomes consistently improve after receiving gender-affirming medical treatment. In many instances, this care is lifesaving treatment.

89. Gender-affirming medical care is also safe and supported by robust evidence comparable to that supporting other medical treatments.

ii. Gender-Affirming Medical Care Is A "Core Medical Service."

90. Gender-affirming medical care qualifies as a "core medical service" under the Ryan White Program. It has long been provided by recipients of Ryan White funding to transgender persons living with HIV/AIDS.

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and Gender-Affirming Care of Transgender and Gender Nonbinary People (Madeline B. Deutsch ed., 2d ed. 2016), https://tinyurl.com/cbhjzchs [https://perma.cc/X5SJ-JKCX] (revision forthcoming).

[24] *E.g.*, Michael Horberg et al., *Primary Care Guidance for Providers Who Care for Persons With Human Immunodeficiency Virus: 2024 Update by the HIV Medicine Association of the Infectious Diseases Society of America*, Clinical Infectious Diseases, (2024), https://doi.org/10.1093/cid/ciae479; Int'l Advisory Panel on HIV Care Continuum Optimization, *IAPAC Guidelines for Optimizing the HIV Care Continuum for Adults and Adolescents*, 14 J. Intn'l Assoc. Providers AIDS Care, Suppl. 1, S3-S34 (2015), https://tinyurl.com/ynr2p2dm [https://doi.org/10.1177/2325957415613442].

[25] U.S. Dep't of Health and Hum. Servs, Panel on Antiretroviral Guidelines for Adults and Adolescents, *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* (Sep.12, 2024) (Attached as **Exhibit F**).

91. Congress has repeatedly made clear that it enacted Ryan White to fund a wide array of core medical services for persons living with HIV that may or may not be tailored to specifically treat HIV itself.

92. The Ryan White statute defines "core medical services" to include "outpatient and ambulatory health services." *See* 42 U.S.C. §§ 300ff–14(b)(1), 300ff–22(b)(1), 300ff–51(c). These services include treatment for "co-occurring conditions" of individuals living with HIV. *Id.* §§ 300ff–14(c), 300ff–22(b), 300ff–51(c).

93. And in the 2006 Ryan White reauthorization, Congress ensured that the definition of outpatient and ambulatory services encompassed the broad range of treatment and care necessary to address the health needs of people living with HIV. *See* H.R. Rep. No. 109-695, at 2, 4 (2006). The legislative purpose of these provisions is to fund "primary health care and support services that enhance access to and *retention* in care." *Id.* at 2 (emphasis added).

94. Congress has additionally explained that "the provision of funds for medical case management, including treatment adherence services, [is] a core medical service." H.R. Rep. No. 109-695, at 4 (2006). Indeed, Congress specifically provided "additional guidance to its intent regarding the application of the core medical services requirement and services that may or may not fall within the defined list of core medical services," explaining that a "core medical service in Parts A, B, and C shall include funding case management services that increase access to and retention in medical care." *Id.*

95. HRSA has defined outpatient and ambulatory health services as "diagnostic and therapeutic-related activities [provided] directly to a client by a licensed health care provider in an outpatient medical setting."[26] HRSA policy states that allowable activities include the "treatment

[26] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Ryan White HIV/AIDS Program Services Report Manual* 111 (2025).

and management of physical and behavioral health conditions" and "[p]rescription and management of medication therapy."[27] These definitions encompass a wide range of services delivered in outpatient settings, including ongoing therapeutic interventions and medication management.

96. Many forms of gender-affirming medical care, including gender-affirming hormone therapy, clinical monitoring, and related medical services, are provided in outpatient settings by licensed providers.

97. For transgender people living with HIV, gender-affirming medical care addresses co-occurring conditions (namely, gender dysphoria, and often-times other associated co-occurring mental health conditions, like depression and anxiety resulting from gender dysphoria) that affect the health of such individuals living with HIV.

98. In addition, providing gender-affirming medical care is crucial to enhancing access to and retention in HIV medical care, and accordingly falls under the broad Ryan White mandate.

99. Indeed, access to healthcare that respects and affirms a patient's gender identity generally and gender-affirming medical care particularly are essential and evidence-based components of comprehensive HIV prevention and treatment for transgender individuals. Federal public health authorities have expressly recognized that "[p]roviding gender-affirming care is an important strategy to effectively address the health and medical needs of transgender people with HIV."[28]

100. As HRSA has previously recognized, patients are more likely to be engaged and stay in treatment "[w]hen primary and behavioral health services are located within the same

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[27] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., Policy Notice 16-02 at 7–8 (2016).

[28] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Gender-Affirming Care in the Ryan White HIV/AIDS Program* 1 (Dec. 16, 2021), https://tinyurl.com/53rv6x8c [https://perma.cc/E86F-69HY].

medical system and facility—also known as a "one-stop shop" approach—or when linkages and referrals to behavioral health services are offered."[29]

101. Gender-affirming medical care directly improves engagement in HIV prevention and treatment. The CDC has found that access to a healthcare provider with whom transgender patients feel comfortable discussing gender-related health needs is associated with increased uptake of HIV testing, pre-exposure prophylaxis, and treatment, as well as improved clinical outcomes such as viral suppression.[30]

102. Conversely, the absence or denial of gender-affirming medical care creates significant barriers to HIV care, undermining both individual and public health outcomes. Transgender individuals face pervasive discrimination in healthcare settings, with federal data showing that many are denied care or receive lower-quality services because of their gender identity. These barriers are directly linked to reduced access to HIV prevention and treatment services and poorer health outcomes.[31]

103. Medical and public health consensus consistently confirms that effective HIV care for transgender populations requires a "comprehensive" and "whole-person" approach that integrates biomedical treatment with interventions addressing social determinants of health, stigma, and gender affirmation.[32]

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[29] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *HRSA CAREAction Newsletter* (Feb. 2018), https://tinyurl.com/he5nzr7b [https://perma.cc/FKR9-TSNA].

[30] Kathryn Lee et al., *Factors Associated with Use of HIV Prevention and Health Care Among Transgender Women—Seven Urban Areas, 2019–2020*, 71 Morbidity & Mortality Wkly. Rep. 673, 673–79 (2022), https://tinyurl.com/asvwvxa3 [https://perma.cc/T8T6-UHNH].

[31] Pamela W. Klein et al., *HIV-Related Outcome Disparities Between Transgender Women Living with HIV and Cisgender People Living with HIV Served by the Health Resources & Services Administration's Ryan White HIV/AIDS Program: A Retrospective Study*, PLOS Medicine (May 28, 2020).

[32] Mary S. Neumann et al., *Comprehensive HIV Prevention for Transgender Persons*, 107 Am. J. Pub. Health 207 (2017).

iii. Gender-Affirming Medical Care Falls Within the Requirement to Provide Comprehensive Services to Underserved Populations.

104. Ryan White funds must be used to support "comprehensive" outpatient health services for individuals living with HIV. 42 U.S.C. § 300ff–23. Grant recipients must ensure that care addresses "the special care and service needs of the populations and subpopulations" served. *Id.* This requirement reflects Congress's intent that care be tailored to the medical and structural needs of specific subpopulations affected by HIV. *See* 42 U.S.C. § 300ff–11. And as Congress has noted, "HIV/AIDS disproportionately affects people in poverty, racial/ethnic populations, and others who are underserved by healthcare and prevention systems." H.R. Rep. No. 109-695, at 2 (2006).

105. The Ryan White statute requires prioritization of such underserved and disproportionately affected populations. 42 U.S.C. §§ 300ff–12(b)(1), 300ff–12(b)(4)(B)(ii).

106. Transgender people—particularly transgender women of color—are among the populations most disproportionately affected by HIV in the United States.[33]

107. Accordingly, Ryan White recipients must design services that are aimed at reaching and retaining transgender individuals in care. *See* 42 U.S.C. § 300ff–12(b)(4)(B)(ii).

108. The Ryan White Program emphasizes continuity of care and retention in treatment as core program goals. *See* 42 U.S.C. § 300ff–81. The Senate Report that accompanied the enactment of the Ryan White statute explains that planning bodies may seek information about "the types of specialized services needed to bring vulnerable subpopulations into care and to retain them in care." S. Rep. No. 106-294, at 17 (2000). And the purpose of the 2006 reauthorization was

[33] *See, e.g.*, Centers. for Disease Control & Prevention, *HIV Surveillance Report Diagnoses, Deaths, and Prevalence of HIV in the United States and 6 Territories and Freely Associated States*, 2022(2023), https://tinyurl.com/2nmm4kf5 [https://perma.cc/XRN7-38PB].

to address unmet needs by funding services that "enhance access to and retention in care." H.R. Rep. No. 109-695, at 2; *see also id.* at 15.

109. Because under the Ryan White Program, support and medical services must facilitate comprehensive care, providing gender-affirming medical care is consistent with Congress's multiple mandates to target funding to effectively reach, treat, and retain in care members of vulnerable and historically underserved communities.

C. The Federal Government Has Previously Recognized that Gender-Affirming Medical Care Is Covered by the Ryan White Program.

110. Defendants HHS and HRSA have expressly observed that gender-affirming medical care is an important component of medical care for transgender people living with HIV and falls within the ambit of care covered by Ryan White.

111. On December 16, 2021, HRSA issued a Program Letter that stated that "RWHAP [Ryan White Program] funds may be used to support gender affirming care across various HRSA RWHAP core medical and support service categories."[34] In the letter, HRSA further recognized that providing gender-affirming medical care is "an important strategy to effectively address the health and medical needs of transgender people with HIV."

112. The agency has further recognized that gender-affirming medical care improves engagement in HIV care and supports retention in treatment.

113. As HRSA explained, gender affirmation includes medical interventions (such as hormone therapy and surgeries), social components (such as use of correct names and pronouns), and psychological components, all of which may be necessary to support positive health outcomes.

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[34] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Gender Affirming Care and the Ryan White HIV/AIDS Program* (Dec. 16, 2021), https://tinyurl.com/53rv6x8c [https://perma.cc/E86F-69HY].

114. HRSA further emphasized that Ryan White providers may deliver gender-affirming medical care through multiple service categories, including core medical services and support services.

115. HRSA's guidance reflects the agency's interpretation that providing gender-affirming medical care is consistent with Ryan White's statutory purpose of improving access to care, retention in treatment, and clinical outcomes for people living with HIV.

D. Ryan White Planning Bodies Across the Country Have Identified Serving Transgender People and Providing Gender-Affirming Medical Care as Priorities in HIV Treatment.

116. Ryan White Part A Planning Councils and Part B Consortia are congressionally mandated entities responsible for organizing and directing the delivery of HIV care under the Ryan White Program. These bodies are tasked with assessing the needs of people living with HIV within their communities, establishing service priorities, and allocating federal funds to ensure access to comprehensive, medically appropriate care for people living with HIV. *See* 42 U.S.C. § 300ff–12(b)–(d), § 300ff–27(b).

117. To make these determinations, the Ryan White statute requires the Planning Councils and Consortia to conduct comprehensive needs assessments, evaluate epidemiological trends, assess gaps in care, and incorporate input from people living with HIV and affected communities. *See* 42 U.S.C. § 300ff–12(b)(4).[35]

118. Across multiple jurisdictions nationwide, Ryan White planning bodies and statewide HIV plans identify transgender people as a population disproportionately affected by HIV and incorporate strategies intended to improve engagement in care for transgender people

[35] Health Res. & Servs. Admin., & Centers for Disease Control & Prevention, *Integrated HIV Prevention and Care Plan Guidance, Including the Statewide Coordinated Statement of Need*, CY 2022–2026 2–5 (2020), https://tinyurl.com/2kp4abj2 [https://perma.cc/UD5R-MC5S].

living with HIV, including through the provision of gender-affirming medical care. These plans commonly discuss barriers such as stigma, discrimination, housing instability, and lack of provider competency, and many include strategies relating to culturally responsive care, integrated service delivery, workforce training, and coordination with gender-affirming healthcare services.

119. Statewide and local Ryan White planning documents in Massachusetts,[36] Oregon,[37] California,[38] Arizona,[39] New York,[40] Texas,[41] Florida,[42] Louisiana,[43] Alabama,[44] and Washington,[45] as well as local jurisdictions including Boston,[46] Portland,[47] San Francisco,[48] Los Angeles,[49] San

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[36] Mass. Dep't of Pub. Health et al., *Massachusetts Integrated HIV/AIDS Prevention and Care Plan: HIV/AIDS Services in the Commonwealth: 2017-2021*, https://tinyurl.com/4euy2udp [https://perma.cc/UV3J-AYLP] (last visited May 13, 2026).

[37] Or. Health Auth. et al., *Oregon's 2022-2026 Integrated Plan and Statewide Coordinated Statement of Need* (2022), https://tinyurl.com/3cjxr4fj [https://perma.cc/H5A5-KMHW].

[38] Cal. Dep't of Pub. Health Off. of AIDS, *Ending the HIV Epidemic: California Consortium for CDC PS19-1906*, https://tinyurl.com/mtfbkm96 [https://perma.cc/U67V-HE28] (last visited May 13, 2026).

[39] Ariz. Dep't of Health Servs., *Arizona HIV/STI/HEP C Integrated Plan 2022-2026* (2022), https://tinyurl.com/2pncs8k3 [https://perma.cc/LV62-F2JQ] (last visited May 13, 2026).

[40] N.Y.C. Health Dep't, *Application for Grant Funding* (2020), https://tinyurl.com/5dauxze2 [https://perma.cc/TH4Q-EVMH] (last visited May 13, 2026).

[41] Texas HIV Syndicate., *Achieving Together: A Community Plan to End the HIV Epidemic in Texas* (2018), https://tinyurl.com/4hb29p65 [https://perma.cc/F4BL-VSJ8] (last visited May 13, 2026).

[42] Fla. Dep't of Health et al., *State of Florida Integrated HIV Prevention and Care Plan* (2023) https://tinyurl.com/4y5mfwh8 [https://perma.cc/ELN6-VGFR].

[43] La. Dep't of Health, et al., *Louisiana Integrated HIV Prevention and Care Plan Including the Statewide Coordinated Statement of Need CY 2022–2026* (2022), https://tinyurl.com/jwr9xvt5 [https://perma.cc/6M5T-VDSX] (last visited May 13, 2026).

[44] Ala. Dep't of Pub. Health, *Integrated HIV Prevention and Care Plan* (2022), https://tinyurl.com/2kr2kr76 [https://perma.cc/KCT8-8H4L].

[45] Wash. State Dep't of Pub. Health, *Washington State Integrated HIV Prevention and Care Plan CY 2022-2026* (2022), https://tinyurl.com/2afu6ven [https://perma.cc/6JZC-TAR2].

[46] Bos. EMA Ryan White Plan. Council & Boston Pub. Health Comm'n, *Boston EMA Ryan White Part A: Integrated HIV Prevention and Care Plan 2017-2021*, https://tinyurl.com/mrxy5a2d [https://perma.cc/HXX5-CWTQ] (last visited May 13, 2026).

[47] *Supra* note 37.

[48] S.F. Dep't of Pub. Health, *San Francisco's Integrated Ending the Epidemics Plan 2024-2026 (2024) Strategies and Activities*, https://tinyurl.com/4hvmze5x [https://perma.cc/B82X-HE7B] (last visited May 13, 2026).

[49] Cnty. of L.A. Pub. Health et al., *Los Angeles County Integrated HIV Prevention and Care Plan, 2022-2026* (2022), https://tinyurl.com/552z3uah [https://perma.cc/2PUL-NDFG].

Diego,[50] Seattle,[51] Austin,[52] Dallas County,[53] and Fort Worth/Arlington/Tarrant County,[54] identify transgender communities as priority populations and/or populations disproportionately affected by HIV.

120. Several jurisdictions additionally note the importance of gender-affirming healthcare in connection with HIV service delivery. For example, Massachusetts's Integrated HIV Prevention and Care Plan discusses aligning HIV prevention, care, and treatment services with gender-affirming healthcare services and references provider education relating to hormone therapy and HIV treatment.[55]

121. New York City Ryan White planning materials reference gender-affirming counseling and linkages to gender-affirming medical care.[56] Arizona's statewide HIV planning documents reference provider education relating to gender-affirming medical care.[57]

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[50] San Diego HIV Plan. Grp. et al., *Getting to Zero: 2019 Update to San Diego County's Integrated Plan for HIV Care, Prevention, Testing and Surveillance* (2019), https://tinyurl.com/yc6874wy [https://perma.cc/N4SH-PXUF].

[51] *Supra* note 45.

[52] Austin Area Comprehensive HIV Plan. Council, *Integrated HIV Prevention and Care Plan 2017-2021* (2016), https://tinyurl.com/2u4zazb6 [https://perma.cc/QHW4-YHNH] (last visited May 13, 2026).

[53] Community Solutions, Inc., *Dallas Regional Integrated HIV Prevention and Care Plan CY 2022-2026* (2022), https://tinyurl.com/3u5mbe8k [https://perma.cc/F7T6-KYVS].

[54] North Central Texas HIV Planning Council, *CY 2022 to 2026 Integrated HIV Prevention and Care Plan: Fort Worth-Arlington Transitional Grant Area* (2022), https://tinyurl.com/48ew4cxu [https://perma.cc/J9FF-JGYJ].

[55] Mass. Dep't of Pub. Health, Bureau of Infectious Diseases and Lab'y Scis., *Mass. Integrated HIV/AIDS Prevention and Care Plan. HIV/AIDS Services in the Commonwealth: 2017-2021* 66-70, 77-79 (2016): *accord* https://tinyurl.com/4freeh6k [https://perma.cc/3F8S-45VB]. Bos. Pub. Health Comm'n, *Boston EMA Ryan White Part A: Integrated HIV Prevention & Care Plan 2017-2021* 18 (2016) https://tinyurl.com/mrxy5a2d [https://perma.cc/3SZN-W5L8].

[56] N.Y. HIV Health & Hum. Servs. Planning Council, Needs Assessment Comm., *Achieving Gender Affirming Care in the Ryan White Part A Portfolio* (2018)10–13, https://tinyurl.com/838cuteb [https://perma.cc/YZ49-QJQG].

[57] Ariz. Dep't of Health Servs., *Arizona HIV/STI/Hep C Integrated Plan: 2022-2026* (2022), 4, https://tinyurl.com/2pncs8k3 [https://perma.cc/WYD4-P8WK].

122. Local planning materials from entities in Los Angeles and San Diego similarly discuss integrating gender-affirming medical care into HIV-related service delivery and provider training.[58]

123. Ryan White and HIV planning materials from jurisdictions in Texas likewise reference gender-affirming medical care and transgender-focused HIV services, including the Dallas County Ryan White Standards of Care, which address gender-affirming medical care, and the Austin Ryan White provider trainings concerning gender-affirming medical care and HIV.[59]

124. Florida, Louisiana, and Alabama integrated HIV planning materials similarly identify transgender populations as communities disproportionately affected by HIV and discuss culturally competent care, stigma reduction, workforce education, and barriers to care affecting transgender individuals living with HIV.[60]

125. The aforementioned examples do not account for all the HIV and Ryan White planning bodies that, consistent with the Ryan White Program's purpose to comprehensively provide for the health needs of people living with HIV, have provided guidance and set forth priorities that account for the needs of transgender people living with HIV, including gender-affirming medical care when indicated. Numerous additional statewide and local HIV planning bodies, Ryan White planning councils, and integrated HIV prevention and care plans similarly recognize transgender communities, discuss barriers to care affecting transgender individuals

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[58] L.A. Cnty. Comm'n on HIV, Planning Committee Meeting Minutes (Oct. 21, 2025); San Diego HIV Health Servs. Planning Council, *Practice Guidelines for the Care of Persons Living with HIV/AIDS* (Sept. 22, 2021), https://tinyurl.com/3btnrs69 [https://perma.cc/L7T6-AMDR].

[59] Dallas Cnty. Health & Hum. Servs., *FY 2025 Standards of Care & Service Delivery Guidelines* (2025), https://tinyurl.com/y924sasv [https://perma.cc/7YCK-EZHF]; Admin. Agency, Report Submitted to the Austin Area Comprehensive HIV Planning Council, (Oct. 24, 2024), https://tinyurl.com/zhpd7xza [https://perma.cc/8RHU-KJQM].

[60] Fla. Dep't of Health, *supra* note 42; La. Dep't of Health, *supra* note 43; Ala. Dep't of Pub. Health, *supra* note 44.

living with HIV, and incorporate strategies relating to gender-affirming healthcare services as part of effective HIV care delivery.[61]

E. The Ryan White Program Is a Public Health Success.

126. By authorizing broad categories of medical and support services and empowering local planning bodies and providers to direct resources how and where they are most needed, Congress created one of the most successful public health programs in the Nation's history.[62]

127. As of 2024, the Program had achieved "record-breaking" viral suppression rates exceeding 90% among clients receiving medical care – far above national averages.[63]

128. The program has achieved such success that scholars and healthcare experts have likewise described it as an "exemplar" for chronic disease management models addressing conditions and other complex chronic illnesses because of its integrated care structure and coordinated support services.[64]

129. The Program's success stems from preserving the very statutory structure Congress enacted: flexible, locally responsive, comprehensive systems of care designed to meet all the primary care and HIV-specific health needs of people living with HIV.

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[61] *See*, *e.g.*, Pamela W. Klein et al., *HIV-related Outcome Disparities Between Transgender Women Living with HIV and Cisgender People Living with HIV Served by the Health Resources and Services Administration's Ryan White HIV/AIDS Program*, PLOS Medicine (2020).

[62] *See* David A. Reznik et al., *Documenting Successes 30 Years After Passage of the Ryan White CARE Act*, 32 J. Health Care Poor & Underserved 5 (2021), https://tinyurl.com/2h2dhttp [https://perma.cc/6LU5-24EF]

[63] *See* Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Ryan White HIV/AIDS Program Achieves Record-Breaking Viral Suppression Rate Among Its More Than 576, 000 Clients* (Dec. 2, 2024), https://tinyurl.com/yjj72yba [https://perma.cc/E4FX-3Y6Y].

[64] *See* Jesse C. Thomas et al., *The Ryan White HIV/AIDS Program: An Innovative Model for Chronic Care Delivery*, JAMA (2015), https://tinyurl.com/yh43k5w4 [https://perma.cc/7GNL-2FRZ].

III. The Trump Administration's All-Encompassing Attacks Against Transgender People

130. From its very first day office, the Trump Administration has engaged in a wide-ranging campaign to exclude transgender people from public life and deny them access to the healthcare that enables them to live authentically.

131. The Administration has employed countless levers to erase any mention or recognition of transgender people from and by any part of the federal government and has demanded the same from every federal funding recipient.

132. For example, on January 20, 2025, President Trump issued Executive Order 14168, *Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government*, 90 Fed. Reg. 8650 (Jan. 20, 2025) ("Gender Order"), a cross-cutting effort to reverse existing protections and deny recognition of transgender people's existence.

133. The Gender Order expresses a disparaging, demeaning, idiosyncratic, and unscientific viewpoint about transgender people and gender identity, denying that transgender people exist, deeming them "false," ordering their exclusion from government recognition and protection in numerous aspects of their lives, and demanding that others do the same.

134. Section 2(a) of the Gender Order states that a person's "sex" is an "immutable biological classification as either male or female" and that it "does not include the concept of 'gender identity.'" Section 2 of the Gender Order establishes that it is the "policy of the United States to recognize two sexes, male and female," which "are not changeable and are grounded in fundamental and incontrovertible reality."

135. Section 2 of the Gender Order defines what it terms "gender ideology" as "replac[ing] the biological category of sex with an ever-shifting concept of self-assessed gender identity, permitting the false claim that males can identify as and thus become women and vice

versa, and requiring all institutions of society to regard this false claim as true. Gender ideology includes the idea that there is a vast spectrum of genders that are disconnected from one's sex. Gender ideology is internally inconsistent, in that it diminishes sex as an identifiable or useful category but nevertheless maintains that it is possible for a person to be born in the wrong sexed body."

136. In addition, Section 2 of the Gender Order defines what it terms "gender identity" as "reflect[ing] a fully internal and subjective sense of self, disconnected from biological reality and sex and existing on an infinite continuum, that does not provide a meaningful basis for identification and cannot be recognized as a replacement for sex."

137. Section 3(e) of the Gender Order demands that agencies "take all necessary steps, as permitted by law, to end the Federal funding of gender ideology."

138. Section 3(g) of the Gender Order prohibits the use of federal funds "to promote gender ideology" and directs each agency to "assess grant conditions and grantee preferences and ensure grant funds do not promote gender ideology."

139. The Gender Order further mandated all federal agencies to interpret sex-based terms as birth-assigned sex, including with regard to government-issued identification documents and personnel records, § 3(c), (d); rescinded provisions of prior executive orders combating discrimination against LGBTQ people, § 7(b); mandated housing in accordance with a person's birth-assigned sex in federal prisons and federally-funded shelters, § 4; and directed federal agencies to rescind guidance, forms, and policies acknowledging the existence of transgender people, §§ 3(e), 7(c).

140. Also on January 20, 2025, President Trump issued Executive Order 14148, *Initial Rescissions of Harmful Executive Orders and Actions*, 90 Fed. Reg. 8237 (Jan. 20, 2025), which

rescinded several Biden Administration Executive Orders that provided protections for transgender people.

141. On January 27, 2025, President Trump then issued Executive Order 14183, *Prioritizing Military Excellence and Readiness*, 90 Fed. Reg. 8757 (Jan. 27, 2025) ("Military Ban Order"), banning transgender people from serving in the military, and revoked Executive Order 14004, which had allowed all qualified persons to serve in the military. As justification, President Trump declared that "expressing a false 'gender identity' divergent from an individual's sex cannot satisfy the rigorous standards necessary for military service" and "is not consistent with the humility and selflessness required of a service member."

142. On January 28, 2025, President Trump also issued Executive Order 14187, *Protecting Children From Chemical and Surgical Mutilation*, 90 Fed. Reg. 8771 (Jan. 28, 2025) ("Denial-of-Care Order"), declaring that "it is the policy of the United States that it will not fund, sponsor, promote, assist, or support the so-called 'transition' of a child from one sex to another," and directing the immediate defunding of medical institutions that provide gender-affirming medical care to transgender people under the age of nineteen.

143. Additional Executive Orders followed, with the Administration using the power of the purse to enforce its erasure of transgender people and its refusal to recognize any form of systemic discrimination; threatening federal funding for schools that recognize and affirm transgender students' identities; and barring transgender athletes from school sports. *See*, *e.g.*, Exec. Order 14151, *Ending Radical and Wasteful Government DEI Programs and Preferencing*, 90 Fed. Reg. 8339 (Jan. 20, 2025); Exec. Order 14173, *Ending Illegal Discrimination and Restoring Merit-Based Opportunity*, 90 Fed. Reg. 8633 (Jan. 21, 2025); Exec. Order 14190,

Ending Radical Indoctrination in K-12 Schooling, 90 Fed. Reg. 8853 (Jan 29, 2025); Exec. Order 14201, *Keeping Men Out of Women's Sports*, 90 Fed. Reg. 9279 (Feb. 5, 2025) ("Sports Ban EO").

144. These Executive Orders employ dehumanizing, inaccurate rhetoric to cast transgender people, gender-affirming medical care, and transgender-inclusive policies as an existential threat to "the validity of the entire American system," Gender Order § 1, as antithetical to "an honorable, truthful, and disciplined lifestyle," lacking "humility and selflessness," Military Ban Order § 1, and as a source of "endangerment, humiliation, and silencing of women and girls," Sports Ban Order § 1.

145. Far from mere policy preferences, courts have recognized that these Executive Orders, particularly the Gender Order, seek to erase transgender people and punish the organizations that provide them necessary services and care.[65]

146. Federal agencies have taken immediate and continuous actions, pursuant to the Gender Order, to carry out the Administration's campaign against transgender people.

147. The Office of Management and Budget promised to stop the use of federal funds to promote "transgenderism."[66] The Office of Personnel Management (OPM) instructed federal agencies, including HHS and HRSA, to "[t]ake down all outward facing media (websites, social media accounts, etc.) that inculcate or promote gender ideology."[67]

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[65] *See*, *e.g.*, *Endocrine Soc'y v. Fed. Trade Comm'n*, No. 26-cv-00512-JEB, 2026 WL 1257289, at *2 (D.D.C. May 7, 2026); *PFLAG, Inc. v. Trump*, 769 F. Supp. 3d 405, 443–44 (D. Md. 2025); *San Francisco A.I.D.S. Found. v. Trump*, 786 F. Supp. 3d 1184, 1215–16 (N.D. Cal. 2025); *Orr v. Trump*, 778 F. Supp. 3d 394, 417–18 (D. Mass. 2025), *appeal pending*, No. 25-1579 (1st Cir.).

[66] Memorandum from Matthew J. Vaeth, Acting Director, Off. of Mgmt. & Budget, *Temporary Pause of Agency Grant, Loan, and Other Financial Assistance Programs* (Jan. 27, 2025), https://tinyurl.com/3zpchy7r [https://perma.cc/6UM5-XBV8].

[67] Memorandum from Charles Ezell, Acting Director, U.S. Off. of Pers. Mgmt., *Initial Guidance Regarding President Trump's Executive Order Defending Women* (Jan. 29, 2025), https://tinyurl.com/243c49d6 [https://perma.cc/M2HN-SRLY].

148. Agencies have removed references to transgender people from government websites. Among the materials removed, altered, or rendered inaccessible were webpages containing statistics regarding HIV among transgender people, HIV testing resources tailored to transgender communities, and datasets used by researchers and providers to monitor HIV transmission and health disparities.[68]

149. For example, large amounts of public information about HIV and the health of teens, transgender, and LGBTQ people abruptly disappeared from CDC websites, including materials relating to HIV diagnoses, HIV prevention, and LGBTQ health disparities.[69]

150. Researchers and scientists have also been ordered to remove any mention of transgender people or recognition of gender identity from any federally funded research,[70] and have had federally funded studies pulled or suspended for simply mentioning transgender people.[71]

151. Agencies have likewise sought to end access to gender-affirming medical care, which enables the transgender people who need it to live authentically, as well as to punish those who express affirming viewpoints about gender-affirming medical care.

152. For example, OPM issued a program carrier letter regarding the Federal Employees Health Benefits Program decreeing that "chemical and surgical modification of an individual's sex

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[68] *See* Ahmed Steenhuysen & Ted Hesson, *U.S. Health Agencies Scrub HIV, Other Data to Remove 'Gender Ideology'*, Reuters (Feb. 1, 2025), https://tinyurl.com/4jfvfhts [https://perma.cc/YK9S-NGQH]

[69] *See* Sophie Gardner, *Public Health Information Pulled Offline in Response to Trump Orders*, Politico (Jan. 31, 2025), https://tinyurl.com/yrktcxy6 [https://perma.cc/9Z63-K3RT].

[70] *See* Carla K. Johnson, *Health Info Wiped from Federal Websites Following Trump Order Targeting Transgender Rights*, PBS News (Jan. 31, 2025), https://tinyurl.com/3c94xtf6 [https://perma.cc/NY2C-5UZT]; Jeremy Faust, *BREAKING NEWS: CDC Orders Mass Retraction and Revision of Submitted Research Across All Science and Medicine Journals. Banned terms must be scrubbed*., Inside Medicine (Feb. 1, 2025), https://tinyurl.com/5t537e9p [https://perma.cc/YFU8-6SVJ]; Apoorva Mandavilli & Roni Caryn Rabin, *C.D.C. Site Restores Some Purged Files After 'Gender Ideology' Ban Outcry*, N.Y. Times (Feb. 3, 2025), https://tinyurl.com/2ep9x83f; Will Stone and Pien Huang, *Some Federal Health Websites Restored, Others Still Down, After Data Purge*, NPR (Feb. 6, 2025), https://tinyurl.com/58wyv5w8 [https://perma.cc/ZA5Y-3BQE].

[71] Fenit Nirappil, *Trans health, research programs ordered to stop by Trump administration*, The Washington Post (Feb. 4, 2025), https://tinyurl.com/5bay7edt [https://perma.cc/6QJX-V9ZW].

traits through medical interventions (to include 'gender transition' services) will no longer be covered under the FEHB or PSHB Programs," regardless of age.[72] And the federal Bureau of Prisons has eliminated access to gender-affirming medical care and discontinued access to gender-affirming clothing and toiletries for transgender people in its custody.[73]

153. The U.S. Department of Justice ("DOJ") has likewise publicly pronounced its intent to target those who provide and support gender-affirming medical care.[74] Indeed, DOJ has issued administrative subpoenas to more than twenty healthcare institutions across the country whose care for their patients includes gender-affirming medical care.[75] And more recently, DOJ has escalated its efforts by issuing at least two criminal grand jury subpoenas to healthcare institutions providing gender-affirming medical care.[76]

154. The Federal Trade Commission has similarly issued civil investigative demands to medical organizations that acknowledge transgender people's existence and express support for gender-affirming medical care.[77]

155. HHS and Secretary Kennedy, as well as HRSA and Administrator Engels, have taken numerous actions to effectuate this administration's policy to erase transgender people and

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[72] U.S. Off. of Pers. Mgmt., Federal Employees Health Benefits Program Carrier Letter (2025), https://tinyurl.com/247n89dd [https://perma.cc/KWT3-46LC].

[73] *See* U.S. Dep't of Just., Bureau of Prisons, Program Statement, *Management of Inmates with Gender Dysphoria*, No. 5260.01 (Feb. 19, 2026), https://tinyurl.com/3cwbfxxh [https://perma.cc/4ABM-YXMG].

[74] *See*, *e.g.*, FBI (@FBI), X.com (June 2, 2025), https://tinyurl.com/5966hpdc [https://perma.cc/6WRE-RZRG]; Memorandum from Brett A. Shumate to All Civil Division Employees (Jun. 11, 2025), https://tinyurl.com/t88ju6xh [https://perma.cc/D3DB-H7XA]; Memorandum from the Att'y Gen. to Select Component Heads, (Apr. 22, 2025), https://tinyurl.com/y6xcv8jk [https://perma.cc/CG7Z-8HRA].

[75] *See* Jo Yurcaba, *DOJ Subpoenas More Than 20 Doctors and Clinics That Provide Trans Care to Minors*, NBC News (July 10, 2025), https://tinyurl.com/5fa2d853 [https://perma.cc/3C7G-S3MA].

[76] *See* Chris Geidner, *The fight over DOJ's invasive trans care subpoenas is coming to a head*, Law Dork (June 4, 2026), https://tinyurl.com/yx5fjh74; Celine Castronuovo, *DOJ Targets NYU With Criminal Subpoena for Trans Health Records*, Bloomberg Law (May 12, 2026), https://tinyurl.com/3ne88ew4.

[77] *See* Vittoria Elliott, *The FTC Is Ramping Up to Target Transgender Rights*, Wired (Apr. 24, 2026), https://tinyurl.com/3z6uc9mx [https://perma.cc/5HU8-8J6Z].

deny their existence, as well as diminish transgender people's access to the healthcare that they need.

156. On February 19, 2025, HHS published a document titled "Defining Sex: Guidance for Federal Agencies, External Partners, and the Public Implementing Executive Order 14168, Defending Women from Gender Ideology Extremism and Restoring Biological Truth to the Federal Government."[78] The document adopts and mirrors in large part the definitions and language set forth in the Gender Order.

157. In addition, HRSA Administrator Engels has decreed that: "It is a HRSA priority to recognize that a person's sex as either male or female is unchangeable and determined by objective biology, and to ensure its programs accurately reflect science, including the biological reality of sex."[79] In doing so, Administrator Engels referenced and incorporated into HRSA's priorities the aforementioned "Defining Sex" guidance issued by HHS based on the Gender Order.

158. Critically, and particularly relevant to this case, HHS has erased transgender people from its guidelines regarding the medical treatment for people with HIV. Through the Panel on Antiretroviral Guidelines for Adults and Adolescents, HHS regularly publishes and updates the "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV." Prior to 2025, these guidelines contained a section titled "Transgender People with HIV" and the September 2024 version mentioned the term "transgender" 190 times.[80] Yet, and notwithstanding that transgender people are disproportionately affected by HIV, following the Administration's

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[78] U.S. Dep't of Health & Hum. Servs., *Defining Sex: Guidance for Federal Agencies, External Partners, and the Public Implementing Executive Order 14168, Defending Women from Gender Ideology Extremism and Restoring Biological Truth to the Federal Government* (Feb. 19, 2025), https://tinyurl.com/4xjd89m8 [https://perma.cc/L3NP-B25R].

[79] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Advancing HRSA's Mission Through Focused, Accountable Action* (2025), https://tinyurl.com/yc6h2ph6 [https://perma.cc/5TS2-8LE2].

[80] U.S. Department of Health and Human Services, *Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* (September 12, 2024).

decree to erase transgender people, the September 2025 version of the guidelines eliminated the section on "Transgender People with HIV" and contains only 13 mentions of the term "transgender," of which all but one are contained in the titles of cited references.[81]

159. HRSA also removed from all of its websites the December 16, 2021 Program Letter regarding the use of Ryan White funds to support gender-affirming medical care for transgender patients living with HIV. It made the 2021 letter publicly available again only after a court ordered the restoration of websites and other resources that were unlawfully erased. *See Doctors for Am. v. Off. of Pers. Mgmt.*, 766 F. Supp. 3d 39 (D.D.C. 2025). Still, HRSA appended the following disclaimer to the Program Letter: "Disclaimer: Per a court order, HHS is required to restore this website as of 11:59 PM February 14, 2025. Any information on this page promoting gender ideology is extremely inaccurate and disconnected from the immutable biological reality that there are two sexes, male and female. The Trump Administration rejects gender ideology and condemns the harms it causes to children, by promoting their chemical and surgical mutilation, and to women, by depriving them of their dignity, safety, well-being, and opportunities. This page does not reflect biological reality and therefore the Administration and this Department rejects it."

160. On April 7, 2025, HRSA issued a letter to Ryan White Program awardees and stakeholders stating that the December 2021 Program Letter regarding the use of Ryan White funds to support gender-affirming medical care "co-opted the program's patient-centered mission in favor of radical ideological agendas and policies" and constituted "a vehicle for broader social or medical experimentation."[82]

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[81] U.S. Department of Health and Human Services, *Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* (September 25, 2025).

[82] Letter from Thomas J. Engels, Adm'r., Health Res. & Servs. Admin., to Ryan White HIV/AIDS Program Awardees and Stakeholders (Apr. 7, 2026), https://tinyurl.com/4neauwpd [https://perma.cc/K3TZ-HWEF].

161. On January 9, 2026, HRSA issued a new "FY 2026 HRSA General Terms and Conditions," which incorporates the HHS Grants Policy Statement that HHS revised with an effective date of October 01, 2025 and which requires recipients to comply "with Title IX of the Education Amendments of 1972, as amended, 20 U.S.C. §§ 1681 et seq., including the requirements set forth in Presidential Executive Order 14168 titled Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government." HRSA included these requirements notwithstanding a federal court order prohibiting it from doing so.[83]

162. On March 11, 2026, HRSA issued the operative and updated "FY 2026 HRSA General Terms and Conditions" at issue in this case, which are addressed in further detail below.

163. Ultimately, the current Administration, operating as a unitary executive, has engaged in a rapid and coordinated rollback of rights and protections previously afforded to transgender Americans. These actions are meant to express moral disapproval of transgender people and disdain towards those whose gender identity does not match their sex at birth.

IV. Defendants Adopt the Challenged Conditions Giving Effect to the Gender Order.

164. As noted, on March 11, 2026, HRSA adopted the updated "FY 2026 HRSA General Terms and Conditions" ("**Updated FY2026 General Terms**") at issue in this case.[84]

165. The Updated FY2026 General Terms apply to and are incorporated into all federal funding provided through and administered by HRSA, including any funding under the Ryan White Program.

166. The Updated FY2026 General Terms give effect to and implement the Gender Order's directive that federal funding recipients not promote gender ideology by prohibiting

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83 *See Rhode Island Coal. Against Domestic Violence v. Kennedy*, 812 F.Supp.3d 180, 202 (D.R.I. 2025).

84 Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *HRSA General Terms and Conditions of Award* 1–2 (Mar. 11, 2026), https://tinyurl.com/4y9zu5cr [https://perma.cc/GK9K-2FZ4] (Attached as **Exhibit A)**.

federal funding recipients under HRSA-administered programs from acknowledging, affirming, or respecting the identities of transgender people and from using federal funds to provide gender-affirming medical care.

167. The Updated FY2026 General Terms do so in multiple ways.

168. First, the Updated FY2026 General Terms expressly require that funding recipients "[a]pply[] sex-based definitions grounded in biological reality."

169. Second, the Updated FY2026 General Terms require funding recipients to "ensure that all activities funded" under the program be "implemented in a manner consistent with HRSA's mission and strategic priorities."

170. HRSA's "strategic priorities," which the Updated FY2026 General Terms directly link to, specify that: "It is a HRSA priority to recognize that a person's sex as either male or female is unchangeable and determined by objective biology, and to ensure its programs accurately reflect science, including the biological reality of sex."

171. The HRSA strategic priorities further specify that HRSA "will not provide funding under the Ryan-White HIV/AIDS Program (RWHAP) for purposes unrelated to the statute," referencing the April 7, 2025, letter that referred to the affirmation of transgender people's identities and the provision of gender-affirming medical care as "social or medical experimentation" that is part of "radical ideological agendas and policies."

172. Third, the Updated FY2026 General Terms incorporate the HHS Grants Policy Statement that requires federal funding recipients to certify that they are "compliant with Title IX of the Education Amendments of 1972, as amended, 20 U.S.C. §§ 1681 et seq., including the requirements set forth in Presidential Executive Order 14168 titled Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government," and that

they will remain so. This is the same term that HHS and HRSA have been enjoined from including on any notice of award by a federal court in Rhode Island.[85]

173. Further implementing the Gender Order's directive to prohibit federal funding recipients from promoting gender ideology by acknowledging and affirming transgender people's identities, including by providing gender-affirming medical care, HRSA has promulgated discriminatory conditions through Notices of Funding Opportunities ("NOFOs") under the Ryan White Program.

174. A NOFO sets forth the core parameters of a funding opportunity, including applicant eligibility, the purpose and scope of funded activities, application requirements, and evaluation criteria. It also specifies available funding, the period of performance, and the binding terms, conditions, and limitations governing the use of awarded funds.

175. NOFOs define the substantive scope of permissible programmatic services and impose certifications and other requirements as a condition of funding.

176. On November 3, 2025, HRSA released the NOFO for the AIDS Drug Assistance Program ("**ADAP NOFO**"), part of Part B of the Ryan White Program, that provides access to life-saving medications and related services for low-income people living with HIV.

177. The ADAP NOFO provides that "if an ADAP provides sex hormones, it may only allow such hormones to be dispensed to treat HIV/AIDS or prevent the serious deterioration of health arising from HIV/AIDS, rather than for non-statutory purposes such as specified sex-trait modification procedures." The NOFO further states that HRSA "will prioritize funding to States

[85] *See Rhode Island Coal. Against Domestic Violence*, 812 F.Supp.3d at 202; *see also supra*, ¶ 161.

that require clinical documentation and the use of a prior authorization process before sex hormones are approved for dispensing to ADAP clients."[86]

178. On June 8, 2026, HRSA released the NOFO for the Ryan White HIV/AIDS Program Part B States/Territories Supplemental Grant Program ("**Part B Supplemental NOFO**"). The Part B Supplemental NOFO provides that "[a]ll activities proposed in [an] application and budget narrative must align with applicable law, including but not limited to statutes, executive orders, federal regulations and applicable judicial holdings." It further states that discretionary awards "shall not be used to fund, promote, encourage, subsidize, or facilitate . . . denial by the recipient of the sex binary in humans, or the belief that sex is a chosen or mutable characteristic," and warns that applications that do not align with those requirements "will not receive funding to the extent permitted by law and applicable court orders."[87]

179. The Part B Supplemental NOFO also expressly incorporates into its terms the Updated FY2026 General Terms and HRSA Priorities which, among other restrictions, require "[a]pplying sex-based definitions grounded in biological reality."

180. On June 5 and 8, 2026, HRSA also released NOFOs for the Ryan White HIV/AIDS Program Part C Capacity Development Program ("**Part C NOFO**") and the Ryan White HIV/AIDS Program Part F Dental Reimbursement Program ("**Part F NOFO**").[88] The Part C

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[86] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Notice of Funding Opportunity, AIDS Drug Assistance Program (ADAP) Emergency Relief Funds (ERF)*, Opportunity No. HRSA-26-012 (Nov. 3, 2025) https://tinyurl.com/mrynfnsp [https://perma.cc/GEN8-Z7AC].

[87] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Notice of Funding Opportunity, Ryan White HIV/AIDS Program Part B States/Territories Supplemental Grant Program*, Opportunity No. HRSA-26-074 (June 8, 2026) (Attached as **Exhibit B)**.

[88] Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Notice of Funding Opportunity: Ryan White HIV/AIDS Program Part C Capacity Development Program*, Opportunity No. HRSA-26-061 (June 5, 2026) (Attached as **Exhibit C**); Health Res. & Servs. Admin., U.S. Dep't of Health & Hum. Servs., *Notice of Funding Opportunity: Ryan White HIV/AIDS Program Part F Dental Reimbursement Program*, Opportunity No. HRSA-26-085 (June 8, 2026) (Attached as **Exhibit D**).

NOFO and Part F NOFO contain the same terms referenced above as the Part B Supplemental NOFO.

181. Further, NOFOs related to the Ryan White Program are also forecasted for this year, including NOFOS for Ryan White HIV/AIDS Program Part D.[89]

182. Together, the Updated FY2026 General Terms, any similar terms added to Ryan White Program NOFOs, and any other actions implementing the Gender Order with regard to the Ryan White Program constitute the **Challenged Conditions** in this case.

183. The Challenged Conditions, including the Updated FY2026 General Terms, the Part B Supplemental NOFO, the Part C NOFO, and the Part F NOFO, constitute final agency action under the APA, 5 U.S.C. § 704.

184. The Challenged Conditions operationalize and implement the Gender Order, including by mirroring its language, incorporating HHS's "Defining Sex" guidance, and using language that similarly denies the existence of transgender people.

185. The Challenged Conditions require Ryan White funding recipients to discriminate against their transgender patients living with HIV by prohibiting them from acknowledging, affirming, or respecting their transgender patients' identities and prohibiting them from providing gender-affirming medical care to their transgender patients living with HIV, notwithstanding that such care is outpatient care for a co-occurring condition that is permitted under the Ryan White statute.

[89] *Ryan White HIV/AIDS Program Part D – Women, Infants, Children and Youth grant Supplemental Funding*, Grants.gov (May 27, 2026), https://tinyurl.com/5xczkhme [https://simpler.grants.gov/opportunity/c1497685-1cac-4066-8720-ceb122a573a6, archived at https://perma.cc/U4J4-TKWD]; *Ryan White HIV/AIDS Program Part D Coordinated HIV Services and Access to Research for Women, Infants, Children, and Youth (WICY) Existing Geographic Service Areas*, Grants.gov (May 27, 2026), https://tinyurl.com/ycahsv5r [https://perma.cc/36TX-LYXL].

186. The Challenged Conditions are not limited to the provision of direct services. By prohibiting the use of funds to "promote," "encourage," or "facilitate" the recognition that transgender people exist and of the care that they need, the Challenged Conditions extend to patient counseling, care coordination, referrals, and programmatic support. HIV care providers participating in the Ryan White Program are thus placed in the untenable position of either complying with the Challenged Conditions or adhering to accepted medical standards and ethical obligations to their patients.

187. In practical effect, the Challenged Conditions prohibit Ryan White funding recipients from providing affirming HIV care and gender-affirming medical care to their transgender patients, notwithstanding the medical necessity of such care and its well-documented role in effective HIV treatment and retention in care.

V. The Impact of the Challenged Conditions on Plaintiffs and their Transgender Patients Living with HIV

188. If implemented, the Challenged Conditions will cause immediate and irreparable harm to HIV providers, like Provider Plaintiffs and Associational Plaintiffs' members; their transgender patients living with HIV; and the broader public health systems that rely on the Ryan White Program.

189. The Challenged Conditions undermine the integrated model of HIV care that Congress designed the Ryan White Program to support and will force providers like Provider Plaintiffs and Associational Plaintiffs' members to choose between complying with the Challenged Conditions or providing medically necessary care consistent with accepted standards of medicine, their professional medical judgment, their ethical obligations, and state anti-discrimination laws.

190. The Challenged Conditions will also cause Provider Plaintiffs and Associational Plaintiffs' members to undergo significant operational changes, including workflow changes,

service disruptions, staffing adjustments, hiring freezes, delayed procurements, staff layoffs, and program closures.

191. The Challenged Conditions' prohibition on using Ryan White funding for the provision of gender-affirming medical care for transgender patients with HIV will cause transgender patients of Provider Plaintiffs and Associational Plaintiffs' members to lose access to this care, as no source of funding is sufficient to replace the funding provided by the Ryan White Program.

192. The loss of access of gender-affirming medical care will result in adverse health outcomes and negatively affect the health and wellbeing of the transgender patients of Provider Plaintiffs and Associational Plaintiffs in a variety of ways. For example, the loss of access to gender-affirming medical care for these patients will result in exacerbated and untreated gender dysphoria, which in turn can result in severe anxiety and depression, post-traumatic stress disorder, eating disorders, substance abuse, self-harm, and suicidality.

193. Even more broadly, in barring funding recipients from acknowledging, affirming, or respecting their transgender patients' identities in any context, the Challenged Conditions require providers to discriminate against their transgender patients living with HIV in the provision of HIV-specific care and all other care, regardless of whether they are providing gender-affirming medical care.

194. The prohibition on Ryan White funding recipients from acknowledging, affirming, or respecting their transgender patients' identities and providing gender-affirming medical care will negatively affect the HIV care of the transgender patients of Provider Plaintiffs and Associational Plaintiffs' members.

195. The transgender patients of Provider Plaintiffs and Associational Plaintiffs' members largely seek care specifically because providers offer affirming, integrated healthcare in trusted clinical environments. If Plaintiffs are no longer able to provide gender-affirming medical care or are forced to deny or disrespect patients' identities, patients will likely perceive that their providers and the healthcare system are unwilling or unable to meet their basic healthcare needs.

196. This breakdown in trust will cause many transgender patients to disengage from care altogether. Transgender patients who lose access to affirming HIV care and gender-affirming medical care are likely to stop attending appointments, discontinue HIV treatment, avoid healthcare settings, and become disconnected from critical support services. For many patients, particularly those facing structural barriers such as homelessness, poverty, transportation instability, or prior experiences of discrimination, re-engagement in care after disengagement is extremely difficult or impossible.

197. The resulting health consequences will be immediate and severe. Patients who disengage from HIV care experience interruptions in antiretroviral treatment, leading to increased viral load, weakened immune systems, disease progression, opportunistic infections, hospitalization, development of drug resistance, and increased risk of progression to AIDS. Such disruptions in care are also likely to worsen depression, anxiety, trauma, suicidality, and other mental health conditions among transgender patients living with HIV.

198. Patients who lose access to consistent outpatient HIV care are more likely to rely on emergency departments and crisis-based care settings, which are not equipped to provide coordinated HIV treatment. This results in poorer health outcomes, increased healthcare costs, and additional strain on already burdened healthcare systems.

199. These harms are especially acute for the members of Associational Plaintiffs practicing in medically underserved communities, including rural areas, non-Medicaid expansion states, and communities experiencing homelessness. For Associational Plaintiffs' members practicing in non-Medicaid expansion states, the Ryan White Program often serves as the only source of HIV care for low-income transgender patients because many patients have no alternative healthcare coverage. For members practicing in rural areas, transgender patients frequently lack transportation, financial resources, or access to providers competent to provide affirming HIV care or gender-affirming medical care outside of Ryan White-funded HIV clinics. Members practicing at programs serving individuals experiencing homelessness further report that transgender patients experiencing homelessness face severe barriers to maintaining continuity of HIV treatment absent integrated, Ryan White-supported services.

200. The Challenged Conditions also risk causing broader public health harms. Loss of viral suppression among transgender people living with HIV increases the risk of HIV transmission in the broader community, undermining decades of progress in controlling the HIV epidemic and reversing gains in reducing HIV incidence. Interruptions in HIV treatment can also contribute to transmission of drug-resistant HIV strains, creating long-term public health consequences and increasing the complexity and cost of future HIV treatment.

201. The Challenged Conditions are also likely to destabilize HIV care infrastructure nationwide. Provider Plaintiffs and Associational Plaintiffs' members will face operational confusion and uncertainty about how to comply with vague and unworkable restrictions, increasing administrative burden, compliance costs, staffing pressures, and legal risk. Clinics may reduce services, eliminate programs, lay off staff, freeze hiring, delay procurements, or close programs altogether, further limiting access to HIV care for vulnerable populations.

202. HIV care providers, like Provider Plaintiffs and Associational Plaintiffs' members, may also suffer profound moral distress as they are forced to deny medically necessary care to transgender patients living with HIV. These harms exacerbate existing workforce shortages within the HIV care system and threaten the long-term stability of the nation's already depleted HIV workforce. Some providers may even leave the field entirely if forced to comply with the Challenged Conditions.

CLAIMS FOR RELIEF

Count I – Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)(A) Arbitrary and Capricious

203. Plaintiffs restate and reallege each of the foregoing paragraphs as if fully set forth herein.

204. Defendants HHS and HRSA are "agenc[ies]" under the APA. 5 U.S.C. § 551(1).

205. The APA directs courts to "hold unlawful and set aside agency action[s]" that are "arbitrary [and] capricious." 5 U.S.C. § 706(2)(A).

206. Agency action is arbitrary and capricious when it relies on factors which Congress has not intended it to consider, entirely fails to consider an important aspect of the problem, offers an explanation that runs counter to the evidence before the agency, or makes a decision that is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

207. An agency action is also arbitrary and capricious when the action is not based on consideration of the relevant factors that Congress intended the agency to weigh in making its determination.

208. When an agency action deviates from past policy or practice, the agency must provide a more detailed justification than would suffice for a new policy created on a blank slate. Additionally, when the prior policy has engendered serious reliance interests, the agency must

assess those reliance interests, determine whether they were significant, and weigh any such interest against competing policy concerns.

209. Providing a pretextual reason for taking agency action that is incongruent with what the record reveals about the agency's priorities and decision-making process can also be a basis for setting aside agency action as arbitrary and capricious. So can issuing decisions featuring unjustifiable bias or partisanship.

210. The Challenged Conditions are arbitrary and capricious for myriad reasons, any one of which would be sufficient to render them unlawful.

211. *First*, the Challenged Conditions fail to consider the factors relevant to issuing Ryan White funds that will best serve the purposes of the Ryan White CARE Act. Congress structured the Ryan White Program to provide comprehensive care for *all* individuals living with HIV/AIDS—including "those communities and populations that have been historically most underserved, as well as those that are experiencing rapid increases in HIV infection and AIDS case counts." S. Rep. No. 106-294, at 12 (2000). Congress intended Ryan White funds to "improve the quality of life for those infected or affected" by the HIV/AIDS epidemic by strengthening care retention rates, increasing viral suppression, and bettering overall health outcomes. H. Rep. No. 109-695, at 2 (2006). And Congress "recognize[d] and affirm[ed]" that the HIV/AIDS epidemic is "best be addressed through a local process" familiar with "shifting trends in the local epidemic, disparities in health care access and outcomes, and the need for capacity development within the HIV health care infrastructures." S. Rep. No. 106-294, at 13. The Challenged Conditions run roughshod over those Congressional mandates in several respects, as further alleged below and because they ignore that gender-affirming medical care is outpatient care that is covered by the Ryan White Program.

212. *Second*, the Challenged Conditions entirely fail to consider several important aspects of the problem and, in fact, run counter to the evidence before Defendants. The Challenged Conditions ignore the strong medical consensus that gender-affirming medical care is evidence-based and, for many patients living with HIV/AIDS, medically necessary to achieve long-term positive health outcomes for the patient and for the broader community. Similarly, the Challenged Conditions disregard the well-documented links between access to gender-affirming medical care and improved HIV/AIDS-related health outcomes, including continued participation in care and consistent viral suppression. Indeed, the Challenged Conditions go beyond banning the use of Ryan White funding for gender-affirming medical care and prohibit caregivers from in any way acknowledging the existence of transgender people—including, for example, by using their correct pronouns. Congress intended to foster positive medical outcomes for patients living with HIV/AIDS by making it less likely that people living with HIV who rely on the Ryan White Program will discontinue their engagement with their HIV care and fall out of care altogether, but the Challenged Conditions undercut that intention. Finally, the Challenged Conditions ignore that Congress wanted decision-makers rooted in their local communities—not distant federal bureaucrats—to identify, prioritize, and ultimately provide community-specific care to individuals living with HIV/AIDS.

213. *Third*, the Challenged Conditions fail to acknowledge—let alone justify—their departure from Defendants' prior policies regarding the use of Ryan White funding to support gender-affirming medical care. In the December 2021 Program Letter, Defendants told Plaintiffs that "[p]roviding gender-affirming care is an important strategy to effectively address the health and medical needs of transgender people with HIV." Defendants told Plaintiffs that Ryan White funds could be used to help transgender patients receive a variety of forms of gender-affirming

medical care—including "access to gender-affirming hormone therapy"; "purchas[ing] and maintain[ing] private health insurance, Medicaid, and Medicare coverage" that can support the health needs of transgender people with HIV; providing mental health services for individuals suffering from gender dysphoria and the social and emotional stress related to transgender discrimination, stigma, and rejection; and providing housing, case management, and substance use disorder treatment services for transgender individuals. The Challenged Conditions reverse those positions. Yet, the Challenged Conditions fail to reasonably explain that about-face or even acknowledge that Defendants are detouring from a beaten path. This provides an independent basis for finding them to be arbitrary and capricious.

214. *Fourth*, the Challenged Conditions fail to assess whether there were reliance interests, determine whether they were significant, and weigh any such interests against competing policy concerns. Plaintiffs have used Ryan White funds to structure integrated care models to improve retention rates and viral suppression among transgender individuals living with HIV. Caregivers have made significant investments in staffing and facilities to provide holistic care to people living with HIV—offering gender-affirming medical care along with other necessary medical treatment, case management, medical transportation, access to specialists, and hospice care. The Challenged Conditions will disrupt that infrastructure and force caregivers to choose between receiving crucial government support and honoring their commitments to provide the most effective and complete care to their patients. The loss of access to complete and affirming care will also shatter the trust of patients—undermining their important reliance interests, seriously jeopardizing their health and well-being, and damaging the public health goals of controlling the spread of HIV. The Challenged Conditions exacerbate that impact by barring caregivers from

showing transgender patients living with HIV the basic respect of acknowledging their identities, even when providing medical services not banned by the Challenged Conditions.

215. *Fifth*, the Ryan White statute prescribes a degree of separation between the federal government and the entities that disburse Ryan White funding to service providers. The overriding purpose of the statute is to financially enable "public or private nonprofit entities" to "develop[], organiz[e], coordinat[e] and operat[e]" "effective and cost efficient systems" to "deliver[] [] essential services to individuals and families with HIV disease." 42 U.S.C. § 300ff. Accordingly, the Act empowers local Planning Councils and Consortia—not Defendants—to "determine the size and demographics of the population of individuals with HIV/AIDS, as well as the size of and demographics of the estimated population of individuals with HIV/AIDS who are unaware of their HIV status"; to "determine the needs of such population[s]"; and to "establish priorities for the allocation of" Ryan White funding within their communities, including "how best to meet each such priority." 42 U.S.C. § 300ff–12(b)(4)(A)-(C) (Part A). Similarly, the Act directs the Secretary to issue "supplemental grants to States" to "enable *such States*" to provide "comprehensive services" in "emerging communities within the State that are not eligible to receive grants under Part A." 42 U.S.C. § 300ff–30(a) (Part B. Supp.) (emphasis added). Yet the Challenged Conditions disrupt this.

216. All told, the Challenged Conditions are not the products of reasoned decision-making. Defendants have offered no coherent explanation of how these changes serve Congress's purposes in providing Ryan White funding. Nor have they attempted to justify singling out one form of medical treatment from all other forms of HIV-specific and non-HIV-specific medical care that are funded by Ryan White. Instead, they self-evidently reflect unjustifiable bias against the LGBTQ community and rely on pretextual reasons that are incongruent with what the record

reveals about the agency's priorities and decision-making process. The Challenged Conditions thus represent precisely the type of agency action that violates the arbitrary-and-capricious standard.

217. Plaintiffs therefore ask the Court to declare under 5 U.S.C. § 706 that the Challenged Conditions violate the APA because they are arbitrary and capricious; provide preliminary relief staying implementation of the Challenged Conditions under 5 U.S.C. § 705 pending final judgment; and preliminarily and permanently enjoin Defendants from imposing the Challenged Conditions.

Count II – Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)(A)
Not in Accordance with Law

218. Plaintiffs restate and reallege paragraphs 1 through 202 as if fully set forth herein.

219. The APA directs courts to "hold unlawful and set aside agency action[s]" that are "not in accordance with law." 5 U.S.C. § 706(2)(A).

220. The Challenged Conditions contravene critical components of the Ryan White CARE Act.

221. The purpose of the Ryan White CARE Act is to "make financial assistance available to States and other public or private nonprofit entities to provide for the development, organization, coordination[,] and operation of more effective and cost efficient systems for the delivery of essential services to individuals and families with HIV disease" and to "provide emergency assistance to localities that are disproportionately affected by the [HIV/AIDS] epidemic." 42 U.S.C. § 300ff.

222. To achieve that purpose, the Ryan White statute mandates that funding be provided to establish a comprehensive system of care for low-income individuals living with HIV/AIDS who lack sufficient health coverage or financial resources. *See* 42 U.S.C. § 300ff–11(a) (Part A);

42 U.S.C. § 300ff–21 (Part B); *id.* § 300ff–29a (Part B Supp.); *id.* § 300ff–51 (Part C); *id.* § 300ff–71 (Part D).

223. The Ryan White statute also mandates that funding be used to provide "core medical services" and "support services" that improve access to and retention of comprehensive medical care, increase viral suppression, and improve overall health outcomes. *See* 42 U.S.C. § 300ff–14(c) – (d) (Part A); *id.* § 300ff–22(a) (Part B); *id.* § 300ff–29a (Part B Supp.); *id.* § 300ff–51(b) (Part C); *id.* § 300ff–71 (Part D).

224. Core medical services include "outpatient and ambulatory health services," as well as medical care for the treatment of "co-occurring conditions" of patients living with HIV participating in the Ryan White Program. *See* 42 U.S.C. §§ 300ff–14(b)(1), 300ff–22(b)(1), 300ff–51(c).

225. The Challenged Conditions violate the Congressional command to allow for coverage of outpatient and ambulatory health services, including medical care for the treatment of co-occurring conditions like gender dysphoria, by, among other things, prohibiting recipients of Ryan White funding from providing comprehensive care to people living with HIV and imposing restrictions that will indisputably *reduce* rather than *enhance* retention in care for people from underserved populations and will therefore lead to lower viral suppression rates.

226. The Challenged Conditions also violate the Affordable Care Act. *See* 42 U.S.C. § 18001 *et seq.*

Section 1554 of the Affordable Care Act

227. Section 1554 of the Affordable Care Act, also known as the "Noninterference Mandate," prohibits HHS, and its component agencies, from promulgating a regulation or substantive policy that "creates any unreasonable barriers to the ability of individuals to obtain

appropriate medical care," "impedes timely access to health care services," or "limits the availability of health care treatment for the full duration of a patient's medical needs." 42 U.S.C. § 18114.

228. The Challenged Conditions create unreasonable barriers to the ability of transgender Ryan White patients to obtain gender-affirming medical care by prohibiting the use of Ryan White funding for such care notwithstanding that patients that rely on Ryan White do so because they otherwise lack the economic means to obtain necessary medical care. The Challenged Conditions also erect barriers to the ability of transgender Ryan White patients to obtain HIV care by making it less likely that they can obtain comprehensive care from a single provider and requiring that Ryan White funding recipients not acknowledge and respect the identities of their transgender patients.

229. The Challenged Conditions impede timely access to healthcare services by making it more difficult, or even impossible, for transgender Ryan White patients to access the gender-affirming medical care they need.

230. By prohibiting the use of Ryan White funds for gender-affirming medical care notwithstanding the Ryan White Program's purpose to provide people living with HIV with full comprehensive care, including for any co-occurring conditions, the Challenged Conditions limit the availability of healthcare treatment, in this case gender-affirming medical care, for the full duration of a patient's medical needs, in this case gender dysphoria.

Section 1557 of the Affordable Care Act

231. For the reasons described in Count V (Section 1557 of the Affordable Act), paragraphs 247 through 261, which Plaintiffs incorporate by reference as if fully set forth herein,

the Challenged Conditions constitute unlawful discrimination that violates Section 1557 of the Affordable Care Act and are therefore not in accordance with law.

232. Plaintiffs therefore ask the Court to declare under 5 U.S.C. § 706 that the Challenged Conditions violate the APA because they are not in accordance with law; provide preliminary relief staying implementation of the Challenged Conditions under 5 U.S.C. § 705 pending final judgment; and preliminarily and permanently enjoin Defendants from imposing the Challenged Conditions.

Count III – Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)(C)
Exceeds Statutory Authority

233. Plaintiffs restate and reallege paragraphs 1 through 202 as if fully set forth herein.

234. The APA directs courts to hold unlawful and set aside agency actions that exceed the agency's "statutory jurisdiction, authority, or limitations." 5 U.S.C. § 706(2)(C).

235. An agency has no power to act—including under its regulations—unless and until Congress authorizes it do so by statute. Accordingly, any action that an agency takes outside the bounds of its statutory authority is *ultra vires* and violates the Administrative Procedure Act.

236. Nothing in the Ryan White statute or any other legislation authorizes Defendants to impose unauthorized extra-statutory funding conditions that categorically bar recipients from providing gender-affirming medical care for transgender individuals living with HIV under the Ryan White Program or from acknowledging, affirming, and respecting transgender patients' identities.

237. Defendants have thus gone beyond what Congress has permitted it to do.

238. Plaintiffs therefore ask the Court to declare under 5 U.S.C. § 706 that the Challenged Conditions violate the APA because they exceed Defendants' statutory authority; provide preliminary relief staying implementation of the Challenged Conditions under 5 U.S.C. §

705 pending final judgment; and preliminarily and permanently enjoin Defendants from imposing the Challenged Conditions.

Count IV – Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)(B)
Contrary to Constitutional Right, Power, Privilege, or Immunity

239. Plaintiffs restate and reallege paragraphs 1 through 202 as if fully set forth herein.

240. The APA requires courts to "hold unlawful and set aside" any agency action that is taken "contrary to constitutional right, power, privilege, or immunity." 5 U.S.C. § 706(2)(B).

241. For the reasons described in Count VI (Equal Protection), paragraphs 262 through 283, and Count VII (Free Speech), paragraphs 284 through 299, which Plaintiffs incorporate by reference as if fully set forth herein, the Challenged Conditions are contrary to constitutional right.

242. In addition, Article I of the United States Constitution vests Congress with the powers to make laws and control the public fisc. The Presentment Clause provides that "[e]very Bill which shall have passed the House of Representatives and the Senate, shall, before it become a Law, be presented to the President of the United States." U.S. CONST. art. I, § 7, cl. 2. The Appropriations Clause provides that no "[m]oney shall be drawn from the Treasury, but in Consequence of Appropriations made by Law," U.S. CONST. art. I, § 9, cl. 7, and the Spending Clause vests Congress with the power to expend Treasury funds for the "general Welfare of the United States." U.S. CONST. art. I, § 8, cl. 1.

243. What is more, an agency has no power to act unless and until Congress authorizes it to do so by statute. An agency's actions and regulations cannot operate independently of the statute that authorized them.

244. For the reasons described in Count III (Exceeds Statutory Authority), paragraphs 233 through 238, which Plaintiffs incorporate by reference as if fully set forth herein, Defendants have adopted and promulgated the Challenged Conditions without any statutory authority.

245. By adopting and promulgating the Challenged Conditions without any statutory authority, Defendants have violated the separation of powers, and the Challenged Conditions are therefore contrary to constitutional power in violation of the APA.

246. Because Defendants acted beyond the power Congress has conferred upon them, Plaintiffs are entitled to declaratory and injunctive relief, including a declaration under 28 U.S.C. § 2201 that the Challenged Conditions unlawfully exceed Defendants' authority and preliminary and permanent injunctive relief preventing the Challenged Conditions from taking effect or being enforced.

Count V – Violation of the Affordable Care Act, 42 U.S.C. § 18116

247. Plaintiffs restate and reallege paragraphs 1 through 202 as if fully set forth herein.

248. Section 1557 of the Affordable Care Act provides that "an individual shall not . . . be excluded from participation in, be denied the benefits of, or be subjected to discrimination under, any health program or activity, any part of which is receiving Federal financial assistance, . . . or under any program or activity that is administered by an Executive Agency," on the basis of sex. 42 U.S.C. § 18116(a).

249. Section 1557 also prohibits discrimination against an individual or entity based on, inter alia, the sex of an individual with whom the individual or entity has a relationship or association.

250. Defendants HRSA and HHS are covered entities under Section 1557.

251. Discrimination based on transgender status constitutes discrimination on the basis of sex under Section 1557 of the ACA.

252. Withholding healthcare solely because such care is provided for the purpose of aligning a patient's gender presentation with an identity different from their sex assigned at birth

is discrimination based on transgender status, and thus discrimination on the basis of sex under Section 1557 of the ACA.

253. The Challenged Conditions discriminate based on sex by requiring healthcare providers participating in the Ryan White Program to withhold healthcare from their transgender patients for the purpose of gender transition or treatment of their gender dysphoria.

254. The Challenged Conditions discriminate based on sex against the transgender patients to whom the Provider Plaintiffs and Associational Plaintiffs' members provide healthcare. These patients face barriers to asserting their own claims and protecting their own interests.

255. By requiring that Plaintiffs deny gender-affirming medical care to transgender patients as a condition of participating in the Ryan White program, the Challenged Conditions deny Plaintiffs' patients the ability to obtain the same medications, procedures, and comprehensive primary care to which they are entitled under the Ryan White Program, because of their sex.

256. By directing Provider Plaintiffs and Associational Plaintiffs' members to withhold healthcare if it "den[ies] . . . the sex binary in humans" or if it encourages "the belief that sex is a chosen or mutable characteristic," the Challenged Conditions force Plaintiffs to withhold medically necessary healthcare from their patients or to forgo participating in the Ryan White program.

257. By directing Provider Plaintiffs and Associational Plaintiffs' members to deny the existence of transgender people and to refuse to recognize, acknowledge, affirm, or respect the identities of their transgender patients, the Challenged Conditions force Plaintiffs to discriminate based on sex against their transgender patients.

258. Defendants do not have the power to override Section 1557 of the ACA and require Plaintiffs to engage in precisely the discrimination that Section 1557 prohibits.

259. Even if, *arguendo*, the Challenged Conditions were not facial discrimination based on sex, they are the direct product of the Administration's discriminatory animus toward transgender people – disapproval and prejudice rooted in the fact that a transgender person's gender identity does not align with their sex assigned at birth – and therefore operate to deny them access to the care that allows them to live as themselves.

260. Plaintiffs are entitled to a declaration that the Challenged Conditions violate Section 1557 of the ACA.

261. Plaintiffs are further entitled to a preliminary and permanent injunction preventing the Defendants from enforcing or implementing the Challenged Conditions, including incorporating the Challenged Conditions in any notice of award under the Ryan White Program.

Count VI – Violation of the Fifth Amendment
Equal Protection Guarantee

262. Plaintiffs restate and reallege paragraphs 1 through 202 as if fully set forth herein.

263. The Fifth Amendment to the United States Constitution guarantees that no person shall be "deprived of life, liberty, or property, without due process of law."

264. The Fifth Amendment's Due Process Clause makes the Fourteenth Amendment's guarantee of equal protection applicable to the federal government, its agencies, its officials, and its employees.

265. Discrimination because a person is transgender constitutes (1) discrimination based on a sex, which requires courts to apply, at minimum, intermediate scrutiny when evaluating the constitutionality of the government's discrimination, and (2) discrimination based on transgender status, which requires courts to apply heightened scrutiny to such discrimination.

266. Government discrimination against transgender people because of their transgender status bears indicia of a suspect classification requiring heightened scrutiny by the courts:

a. Transgender people have suffered a long history of extreme discrimination, both *de jure* and *de facto*, and continue to suffer such discrimination to this day;

b. Transgender people are a discrete and insular group and lack the political power to protect their rights through the legislative process. Transgender people have largely been unable to secure explicit local, state, and federal protections to protect them against discrimination, and have been and continue to be regularly targeted for discrimination by legislation, regulations, and other government action;

c. A person's gender identity or transgender status bears no relation to a person's ability to contribute to society; and

d. Gender identity is a core, defining trait that is so fundamental to one's identity and conscience that a person cannot be required to abandon it as a condition of equal treatment. Gender identity is also generally fixed at an early age and highly resistant to change.

267. The Challenged Conditions discriminate against Plaintiffs based on sex and transgender status by depriving them of Ryan White funding based on whether they care for transgender people, attend to their transgender patients' health needs, and acknowledge and respect the identities of their transgender patients.

268. The Challenged Conditions also discriminate based on sex and transgender status against the transgender patients to whom Plaintiffs provide healthcare. These patients face barriers to asserting their own claims and protecting their own interests.

269. The Challenged Conditions were issued for the openly discriminatory purpose of expressing governmental disapproval of transgender people and rendering them unequal to others.

They are status-based classifications of persons undertaken for their own sake, something the Constitution's Equal Protection guarantee does not permit.

270. By prohibiting healthcare providers from providing gender-affirming medical care to transgender patients living with HIV using Ryan White funds, the Challenged Conditions intentionally deny Plaintiffs' patients the ability to obtain the same medications and procedures available to other patients, as well as the comprehensive primary care to which they are entitled under the Ryan White Program, because of their sex and transgender status.

271. The Challenged Conditions facially and intentionally discriminate based on sex and transgender status by requiring healthcare providers participating in the Ryan White Program to withhold healthcare from their transgender patients for the purpose of gender transition, that is, helping a patient's gender presentation to align with an identity different from their sex assigned at birth.

272. The Challenged Conditions create a facial classification based on sex because they adopt and direct the espousal of idiosyncratic and unscientific sex-based definitions as a condition of Ryan White funding and direct Ryan White funding recipients not to "promote gender ideology."

273. Similarly, by conditioning Ryan White funding on the adoption of "sex-based definitions grounded in biological reality" and on recipients not promoting "gender ideology," the Challenged Conditions discriminate based on transgender status on their face by expressing a disparaging, demeaning, idiosyncratic, and unscientific viewpoint about transgender people.

274. Where Defendants use "sex-trait modification procedures" as a proxy for transgender status, like HRSA did through the ADAP NOFO, Defendants facially and intentionally discriminate based on sex and transgender status. This is particularly so when Defendants permit Ryan White funds to be used for the same medications and procedures for other patients.

275. Even if, *arguendo*, the Challenged Conditions did not facially classify based on sex and transgender status, they are the direct product of the Administration's discriminatory animus toward transgender people – disapproval and prejudice rooted in the fact that a transgender person's gender identity does not align with their sex assigned at birth – and therefore operate to deny them access to the care that allows them to live as themselves.

276. The Challenged Conditions seek to effectuate the Administration's discriminatory purpose of expressing and effectuating its disapproval of and prejudice towards transgender people because the sex the identify with does not align with their sex assigned at birth and therefore deny them access to the care that allows them to live as themselves.

277. The Challenged Conditions are part and parcel of Defendants' efforts to combat so-called "gender ideology," which the Administration defines as the mere recognition or acknowledgement that a person may identify with a sex that differs from their sex assigned at birth, i.e. a transgender person.

278. The Challenged Conditions lack even a rational or legitimate justification, let alone the exceedingly persuasive one that is constitutionally required.

279. The Challenged Conditions also lack adequate tailoring under any standard of review.

280. The Challenged Conditions were promulgated, adopted, and issued for the openly discriminatory purpose of preventing transgender people from expressing a gender identity different from their sex designated at birth—and expressing governmental disapproval of people who do so—which are not even legitimate governmental interests under any standard of review.

281. The Trump Administration has been clear that its goal is to erase the transgender community from participation in society—an effort that results in the literal denial of equal protection and causes ongoing harm to the Plaintiffs and the people that they serve.

282. Plaintiffs are entitled to a declaration that the Challenged Conditions violate the equal protection component of the Fifth Amendment.

283. Plaintiffs are further entitled to a preliminary and permanent injunction preventing the Defendants from enforcing or implementing the Challenged Conditions, including incorporating the Challenged Conditions in any notice of award under the Ryan White Program.

Count VII – Violation of the First Amendment
Free Speech Clause

284. Plaintiffs restate and reallege paragraphs 1 through 202 as if fully set forth herein.

285. The First Amendment prohibits the government from abridging the freedom of speech. Ordinarily, the government may not regulate speech based on its substantive content or the message it conveys.

286. In the context of federal funding, the government may attach certain conditions to eligibility for that funding, but there are limitations on the types of conditions that the government may attach to federal funds without violating the First Amendment.

287. Funding conditions can result in an unconstitutional burden on First Amendment rights if the condition seeks to leverage funding to regulate speech outside the contours of the program itself or if it seeks to suppress dangerous ideas and restrict speech based on viewpoint absent any relationship to the purpose of the funded program.

288. The Updated FY2026 General Terms that HRSA seeks to attach to funding under the Ryan White Program incorporate the "Defining Sex" guidance issued by HHS implementing the Gender Order.

289. The NOFOs issued in June 2026 expressly refer to the Updated FY2026 General Terms and the HRSA Priorities, and use similar language prohibiting Ryan White funding to "promote, encourage, subsidize, or facilitate . . . denial by the recipient of the sex binary in humans, or the belief that sex is a chosen or mutable characteristic."

290. The Challenged Conditions and the Gender Order on which they rely, taken together, express a disparaging and unscientific view of gender identity, repudiates the existence of transgender people, deems their identities to be false, orders their exclusion from government recognition and protection, and seeks to coerce others to do the same by threatening termination of federal funding and other penalties. This violates the First Amendment in two distinct ways.

291. *First*, through the Challenged Conditions, the government has placed a speech condition on the recipient of the subsidy rather than on a particular program or service—a condition that violates the First Amendment.

292. The Challenged Conditions create a funding condition that does not further the objectives of the Ryan White Program and thus places an unconstitutional burden on the First Amendment rights of Provider Plaintiffs and Associational Plaintiffs' members. Indeed, the Ryan White Program statute has no programmatic message that allows the government to regulate speech concerning "gender" as deemed necessary for the Ryan White Program's legitimate objectives.

293. Rather, the Challenged Conditions seek to coerce and penalize federal funding recipients, including Provider Plaintiffs and Associational Plaintiffs' members, whose speech, trainings, research, and services acknowledge the existence of transgender people and advocate for their equality and respect.

294. *Second*, even in the provision of subsidies, the government may not aim at the suppression of dangerous ideas.

295. Through the Challenged Conditions, the government violates the First Amendment by threatening to withhold benefits for a censorious purpose. The First Amendment does not tolerate the administration of subsidy programs with a censorious purpose.

296. The Challenged Conditions are designed and intended to silence, defund, and otherwise penalize Plaintiffs for acknowledging that transgender people exist and providing them with humanitarian HIV services under the Ryan White Program. Plaintiffs cannot competently provide such services to every patient the Ryan White Program intends to reach without acknowledging people's diverse backgrounds and experiences, including their sex and gender identity.

297. Provider Plaintiffs and Associational Plaintiffs' members, as well as the transgender patients they serve under the Ryan White Program, suffer irreparable harm as a direct result of the HRSA's unlawful imposition of the Challenged Conditions.

298. Plaintiffs are entitled to a declaration that the Challenged Conditions violate the First Amendment's Free Speech Clause.

299. Plaintiffs are further entitled to a preliminary and permanent injunction preventing the Defendants from enforcing or implementing the Challenged Conditions, including incorporating the Challenged Conditions on any notice of award under the Ryan White Program.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court enter judgment in their favor and grant the following relief:

A. A declaration that the Challenged Conditions are unlawful and unconstitutional, including as follows:

   i. The Challenged Conditions violate the APA because they are arbitrary and capricious, not in accordance with law, contrary to constitutional right or power, and in excess of statutory authority;

   ii. The Challenged Conditions violate Section 1557 of the Affordable Care Act;

   iii. The Challenged Conditions violate the right to equal protection of Provider Plaintiffs and Associational Plaintiffs' members, as well as their transgender patients, guaranteed under the Fifth Amendment; and

   iv. The Challenged Conditions violate the right to free speech of Provider Plaintiffs and Associational Plaintiffs' members guaranteed under the First Amendment.

B. Preliminary relief under 5 U.S.C. § 705 temporarily setting aside and postponing the effective date of the Challenged Conditions, and preventing their inclusion in any future notices of funding opportunities and notices of award under any part of the Ryan White Program, including any future funding opportunities;

C. Permanent relief under 5 U.S.C. § 706 holding unlawful and setting aside the Challenged Conditions;

D. Preliminary and permanent injunctive relief enjoining Defendants, including their employees, agents, servants, attorneys, successors and any person or entity in active

concert or participation with them, from implementing, enforcing, effectuating, or giving effect to the Challenged Conditions—or any materially similar policy that prohibits Ryan White funding recipients from acknowledging, affirming, and/or respecting the identities of transgender patients or from providing gender-affirming medical care under the Ryan White Program—against Provider Plaintiffs and Associational Plaintiffs' Members.

E. Waive the requirement for the posting of a bond of security for the entry of temporary and preliminary relief;

F. Award Plaintiffs their reasonable fees, costs, and expenses, including attorneys' fees; and

G. Grant any other and further relief that this Court may deem just and proper.

Dated: June 10, 2026

Respectfully submitted,

/s/ Omar Gonzalez-Pagan

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EXHIBIT A

March 11, 2026

FY 2026 HRSA General Terms and Conditions

These terms and conditions apply to all discretionary awards with funds and award modifications with funds made on or after March 11, 2026.

Compliance with Court Orders: Any term or condition in this Notice of Award (NOA), including those incorporated by reference, that HHS is enjoined by court order from imposing or enforcing shall not apply or be enforced as to any recipient or subrecipient to which that court order applies and while that court order is in effect.

1. Administrative Requirements

You must comply with the laws, policies, and terms and conditions included in your Notice of Award (NOA).

This includes:

- Requirements of the authorizing statutes and implementing regulations for the programs under which your award is funded.
- Appropriations acts provisions.
- Terms and conditions included in the HHS Grants Policy Statement (HHS GPS), which HHS revised with an effective date of October 01, 2025.This includes the requirements of applicable HHS regulations and the Uniform Administrative Requirements, Cost Principles and Audit Requirements for Federal Awards codified at 2 CFR 200 and any successor regulations, policies and requirements.
    - The HHS GPS applies to monetary actions only, including non-competing continuation awards and award modifications that add funding made on or after October 01, 2025. This includes supplements to awards, competing and non-competing continuations. The GPS applies to all HRSA discretionary awards and the requirements flow down to subrecipients.
    - Until a monetary action is processed, the July 24, 2025 GPS applies to your award.
- The HHS Administrative and National Policy Requirements (Appendix D, revised to ensure consistency with all administration policies.
- Requirements included in the Notice of Funding Opportunity (NOFO); and
- Policies specific to the award.

Applicable Regulatory Provisions. This award is subject to any applicable provisions of 2 CFR 200 and 2 CFR 300.

In case of conflicting or inconsistent requirements, follow the order of precedence indicated in the HHS Administrative and National Policy Requirements. This document provides statutory, regulatory, and executive requirements that apply to HHS awards.

We may list exceptions to individual requirements stated above in the NOA.

Use of the terms “federal award,” “award,” and “grant” refers collectively and separately to federal assistance awards, grants, and cooperative agreements, unless otherwise indicated.

Per 2 CFR 25, SAM.gov and Unique Entity Identifier (UEI) registration are required throughout the lifecycle of all HRSA awards.

a. Termination

This award is subject to the termination provisions at 2 CFR 200.340. Pursuant to 2 CFR 200.340, the recipient agrees by accepting this award that continued funding for the award is contingent upon the availability of appropriated funds, recipient satisfactory performance, compliance with the Terms and Conditions of the award, and to the extent authorized by law, a decision by the agency that the award continues to effectuate program goals or agency priorities.

b. Appeals

HRSA affords appeal rights for remedies for non-compliance, including terminations for compliance reasons. See 2 CFR 200.342 for opportunities to object, hearings, and appeals.

c. Subrecipients and Recipients (Pass-Through Entities) Responsibilities

The recipient is the entity that receives a federal award directly from HRSA.

The recipient can give a portion of the direct award to other organizations, called subrecipients, to accomplish the goals and objectives of the award.

In this case, the recipient becomes a pass-through entity and the subrecipient's award is called a subaward.

As a recipient, you must ensure the applicable general terms and conditions stated in this document flow down to subrecipients. See the HHS Administrative and National Policy Requirements.

d. Prior Approval

You must get prior approval for certain items, as stated in 2 CFR 200.308 and 2 CFR 200.407. Examples of items requiring prior approval include:

- Significant rebudgeting of project costs. Significant budget changes require prior approval when:
    - The award exceeds the simplified acquisition threshold (currently $350,000), and
    - The cumulative amount of the transfer exceeds 25 percent of the total budget, including cost share, of the most recent approved award (budget period).
        - Due to programmatic need, HRSA is using the 25 percent threshold for prior approval, instead of the 10 percent threshold cited in the HHS GPS Section 3.1.2.2 (Significant Budget Changes)
- Change of scope. A change in scope can occur when a recipient makes a budget change that cause a project to change substantially.
    - If you are not sure your budget change is beyond the scope, contact your Grants Management Specialist (GMS).
- Rebudgeting funding into a direct cost category not previously requested.

We do not automatically authorize prior approvals under 2 CFR 200.308(g) or 2 CFR 200.308(h):

- We do not waive cost-related or administrative prior approvals unless specifically stated in your NOA. You must submit these as a Prior Approval action via HRSA Electronic Handbooks (EHBs) or GrantSolutions (when HRSA transitions to GrantSolutions).
- Only responses to prior approval requests signed by the Grants Management Officer (GMO) are valid.

If you act based on responses from other officials, you do so at your own risk. We do not consider these responses binding.

f. Funding Restrictions

See your NOA and the HHS Administrative and National Policy Requirements for funding restrictions such as:

- Salary Cap (also see Salary Rate Limitation)
- Gun control
- Anti-lobbying
- Restrictions on abortion
- Ban on funding embryo research
- Limitation on use of funds for promotion of legalization of controlled substances
- Restriction of pornography on computer networks
- Restriction on the purchase of sterile needles
- Prohibition on certain telecommunications and video surveillance services or equipment.

g. Roles and Responsibilities.

To see the roles and responsibilities of the GMS and the Program Official (PO) for your award, visit Manage Your Grant - Administrative Management.

i. Antidiscrimination Laws and Requirements Compliance Certification

By applying for or accepting federal funds from HHS, recipients certify compliance with all federal antidiscrimination laws and these requirements and that complying with those laws is a material condition of receiving federal funding streams. Recipients are responsible for ensuring subrecipients, contractors, and partners also comply.

2. Policy Requirements

The HHS Administrative and National Policy Requirements provide a list of requirements applicable to HHS awards.

a. Conflict of Interest

See the HRSA Federal Financial Assistance Conflict of Interest Policy (COI Policy)

3. Financial Requirements

a. Salary rate limitation (SRL)

See the Salary Cap Summary Table for the latest salary rate limitation.

The HHS salary rate limitation applies to both direct and indirect costs for all applicable HHS awards.

b. Payments

Grant funds must be drawn and Federal Financial Reports (FFR) filed using the HHS Payment Management System (PMS).

The Division of Payment Management, Financial Management Services, Program Support Center, manages PMS and has instructions for obtaining payments.

Submit direct inquiries about payments:
ONE-DHHS Help Desk for PMS Support at 1-877-614-5533 or PMSSupport@psc.hhs.gov.

If you do not have access, complete a PMS Access Form (PMS/FFR Form). If you have any questions about accessing PMS, contact the PMS Liaison Accountant.

c. Program income

Per 2 CFR 200.307, HRSA awards use the additive method for program income earned from your award.

Program income requirements for for-profit recipients are governed by 2 CFR 300.318.

4. Reporting Requirements

Review your NOA, HHS Administrative and National Policy Requirements, and HRSA Manage Your Grant for required reports and method of submission.

a. General Reports may include:

- Federal Financial Reports (FFR)
- Noncompeting Continuation (NCC) Progress Reports
- Tangible Personal Property Report (SF-428) for Equipment and Supplies
- Real Property Report (SF-429)
- Subaward Reporting under the Federal Funding Accountability and Transparency Act (FFATA) reporting at SAM.gov.
- Recipient integrity and performance

b. Audit Reports

- If your organization is a nonprofit organization and is required to have audits in accordance with 2 CFR 200, Subpart F (See 2 CFR 200.501) because it spends $1,000,000 or more in federal funds in one fiscal year, submit the audit reports to the Federal Audit Clearinghouse.
- For-profit organizations required to have audits should submit the audit reports directly to HRSA.

c. Reporting Fraud, Waste, Abuse, and Mismanagement

- The HHS Office of the Inspector General (OIG) maintains a toll-free number (1-800- HHS-TIPS [1-800-447-8477]; TTY: 1-800-377-4950) and website for receiving information concerning fraud, waste, abuse, and mismanagement under HHS programs.

  Additionally, information may be submitted by mail to:

  Office of the Inspector General
  Department of Health and Human Services
  Attn: HOTLINE
  330 Independence Ave., SW
  Washington DC 20201

- Such reports are treated as sensitive material. You can decline to give your name if you choose to remain anonymous.

5. Alignment with HRSA funding priorities

a. General Alignment with HRSA Mission and Strategic Priorities

As a condition of this award, you must ensure that all activities funded under this award are implemented in a manner consistent with HRSA's mission and strategic priorities as authorized by law.

Funded activities must advance HRSA's mission of protecting and improving the health and well-being of Americans. The particular focus is on those who are underserved, medically vulnerable, or live in areas with limited access to care. HRSA's duty is to serve wisely, effectively, and with measurable results that justify every taxpayer dollar invested.

Consistent with HRSA's priorities, in carrying out any funded project, the recipient must adhere to the following principles, where they are consistent with the authority and scope of the award and its activities:

- **Gold Standard Science:** Design and deliver services using gold standard evidence-based and evidence-informed approaches, establish measurable performance goals, and use data to monitor outcomes and drive continuous improvement.
- **Program Integrity and Fiscal Stewardship:** Administer all funds in accordance with applicable federal statutes, regulations, and award conditions. You must maintain strong internal controls to prevent waste, fraud, abuse, and mismanagement of taxpayer dollars.
- **Partnership and Local Leadership:** Coordinate with state, tribal, territorial, local, and community partners to ensure services are tailored to community-identified needs while respecting local decision-making authority.

b. Alignment with Administration Objectives

Recipients must manage any awarded project in accordance with the following objectives in programs authorized to advance them:

Make America Healthy Again (MAHA): HRSA prioritizes the health and well-being of all Americans by supporting common-sense, evidence-based health policies that promote:

- Personal responsibility.
- Strong families and communities.
- Proper nutrition.
- The prevention and management of chronic disease, while ensuring access to high-quality, affordable physical and mental health care.

Child protections, biological integrity, parental rights, and lawful use of funds: HRSA prioritizes safeguarding children's health and safety by:

- Not supporting medical interventions for gender dysphoria in minors that lack a strong evidence base.
- Applying sex-based definitions grounded in biological reality.
- Supporting parental authority, transparency, and choice in education, including school-based health centers that respect parental rights and religious upbringing.
- Ensuring taxpayer funds are not used to promote or support elective abortions, consistent with federal law and the Hyde Amendment.

Advancing evidence-based, merit-driven, and ethically grounded health care: HRSA will prioritize unbiased, transparent science; merit-based workforce opportunities; and programs that demonstrate measurable outcomes, while deprioritizing organizations with:

- Conflicts of interest.
- Ineffective "harm reduction" models.
- Housing-first approaches lacking accountability.
- Activities that facilitate illegal drug use or unsafe medical practices.

Promoting public safety, lawful use of federal funds, and national health priorities: To the extent permitted by law, HRSA will align funding with administration priorities by:

- Supporting ending the HIV epidemic through authorized, evidence-based care.
- Reserving benefits for eligible individuals.
- Discouraging illegal immigration and unsafe community practices.
- Prioritizing recipients that enforce public safety, address serious mental illness and substance use through treatment and recovery, and reduce homelessness responsibly.

c. Enforcement Standards

To the extent permitted by law, HRSA gives priority to states and municipalities for programs to:

- Enforce prohibitions on open illicit drug use.
- Enforce prohibitions on urban camping and loitering.
- Enforce prohibitions on urban squatting.
- Enforce, and where necessary, adopt, standards that address individuals who are a danger to themselves or others and suffer from serious mental illness or substance use disorder, or who are living on the streets and cannot care for themselves. The approach must be through assisted outpatient treatment or by moving them into treatment centers or other appropriate facilities through civil commitment or other available means, to the maximum extent permitted by law.

d. Compliance, Monitoring, and Termination

HRSA will implement these priorities consistent with applicable laws, regulations, court orders, and any required procedures.

- **Ongoing Compliance:** You must demonstrate continuous alignment with these priorities through program design, implementation, reporting, and evaluation throughout the period of performance.
- **Corrective Action:** Failure to meaningfully align funded activities with these requirements may result in the imposition of specific award conditions, additional reporting requirements, or corrective action plans.
- **Termination:** In accordance with 2 CFR § 200.340(a)(4), HRSA may terminate this award in whole or in part, to the extent permitted by law, if it determines that the award no longer effectuates the program goals or agency priorities outlined in these terms.

EXHIBIT B

[1]Notice of Funding Opportunity

Application due Friday, July 10, 2026

HRSA
Health Resources & Services Administration

HIV/AIDS Bureau
Division of State HIV/AIDS Program (DSHAP)

Ryan White HIV/AIDS Program Part B States/Territories Supplemental Grant Program

Opportunity number: HRSA-26-074

1


DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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Before you begin

If you believe you are a good candidate for this funding opportunity, secure your SAM.gov and Grants.gov registrations now. If you are already registered, make sure your registrations are active and up-to-date.

SAM.gov registration (this can take several weeks)

You must have an active account with SAM.gov. This includes having a Unique Entity Identifier (UEI).

See Step 2: Get Ready to Apply

Grants.gov registration (this can take several days)

You must have an active Grants.gov registration. Doing so requires a Login.gov registration as well.

See Step 2: Get Ready to Apply

Apply by the application due date

Applications are due by 11:59 p.m. Eastern Time on Friday, July 10, 2026.

To help you find what you need, this NOFO uses internal links. In Adobe Reader, you can go back to where you were by pressing Alt + Left Arrow (Windows) or Command + Left Arrow (Mac) on your keyboard.

All activities proposed in your application and budget narrative must align with applicable law, including but not limited to statutes, executive orders, federal regulations and applicable judicial holdings. Accordingly, discretionary awards shall not be used to fund, promote, encourage, subsidize, or facilitate: racial preferences or other forms of racial discrimination by the recipient, including activities where race or intentional proxies for race will be used as a selection criterion for employment or program participation; denial by the recipient of the sex binary in humans, or the belief that sex is a chosen or mutable characteristic; illegal immigration; or any other initiatives that compromise public safety. If an application does not align, the application will not receive funding to the extent permitted by law and applicable court orders.

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Review the Opportunity

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Basic Information

Health Resources Services Administration

HIV/AIDS Bureau

Division of State HIV/AIDS Program (DSHAP)

Providing additional funding for HIV/AIDS programs.

Summary

The purpose of the Ryan White HIV/AIDS Program Part B States/Territories Supplemental Grant Program is to provide funding for HIV/AIDS care. Specifically, it adds to formula-based funding provided through the HIV Care Grant Program – RWHAP Part B States/Territories Formula, AIDS Drug Assistance Program (ADAP) Formula, and the ADAP Supplemental Awards Notice of Funding Opportunity (HRSA-22-033).

Funding details

Application types: Competing continuation, New

Expected total available funding in FY 2026: $48,000,000

Expected number and type of awards: 30 grants

Funding range per award: $500,000 to $9,000,000

We plan to fund awards in one 12-month budget period for a total one-year period of performance from September 30, 2026, to September 29, 2027.

The program and awards depend on the appropriation of funds and are subject to change based on the availability and amount of appropriations.

Have questions?
Go to Contacts and Support.

Key facts

Opportunity name: Ryan White HIV/AIDS Program Part B States/Territories Supplemental Grant Program

Opportunity number: HRSA-26-074

Announcement version: Initial

Federal assistance listing: 93.917

Key dates

NOFO issue date: March 11, 2026

Informational webinar: TBD

Application deadline: Friday, July 10, 2026

Expected award date is by: September 30, 2026

Expected start date: September 30, 2026

See other submissions for other time frames that may apply to this NOFO.

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Eligibility

Who can apply

You can apply if you are a state government, including the District of Columbia, domestic territories, and the Freely Associated States, unless your state/territory had an unobligated balance (UOB) of more than 5% of a prior year's formula funds.

Types of eligible organizations

These types of domestic* organizations may apply:

- State governments

*"Domestic" means the 50 states, the District of Columbia, the Commonwealth of Puerto Rico, the Northern Mariana Islands, American Samoa, Guam, the U.S. Virgin Islands, the Federated States of Micronesia, the Republic of the Marshall Islands, and the Republic of Palau.

Individuals are not eligible applicants under this NOFO.

Completeness and responsiveness criteria

We will review your application to make sure it meets these basic requirements to move forward in the competition.

We will not consider an application that:

- Is from an organization that does not meet all eligibility criteria.
- Requests funding above the award ceiling shown in the funding range.
- Is submitted after the deadline.

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Application limits

You may not submit more than one application. If you submit more than one application, we will only accept the last on-time submission.

Cost sharing

Post-award requirements

Before you apply, make sure you understand the requirements that come with an award.

See Step 6: Learn What Happens After Award for information on regulations that apply, reporting, and more.

This program has no cost-sharing requirement. If you choose to share in the costs of the project, we will not consider it during merit review. Recipients agree that once committed, cost sharing amounts are enforceable and subject to reporting and auditing requirements under 2 CFR 200.

Program description

Purpose

This program provides funding under the Ryan White HIV/AIDS Program (RWHAP) Part B States/Territories Supplemental Grant Program. The purpose of this program is to supplement formula-based funding provided through the HIV Care Grant Program — RWHAP Part B States/Territories Formula, AIDS Drug Assistance Program (ADAP) Formula, and the ADAP Supplemental Awards Notice of Funding Opportunity (HRSA-22-033).

States/territories use this supplemental funding in conjunction with RWHAP Part B HIV Care Grant Program funding to develop or increase access to a comprehensive continuum of high-quality care and treatment services for low-income people with HIV.

Background

The Ryan White HIV/AIDS Program

The Ryan White HIV/AIDS Program (RWHAP) has five statutorily defined parts that provide grants to states, cities, counties, local clinics, and community-based organizations. The grants fund medical care, medication, and essential support services, to meet the needs of people with HIV and family members affected by HIV. Together these grants provide a comprehensive system of care to ensure low-income people with HIV have access to services for early diagnosis of HIV, linkage to care, medically appropriate treatment, retention in care, and sustained viral suppression (a very low or undetectable amount of HIV in the blood).

For nearly four decades, the RWHAP has funded services to provide HIV primary health care, medication, and essential support services, including mental health care, transportation, case management, nutrition, and housing. These services support clients to enter and remain in care, access medications, and reach viral suppression, reducing transmission and lowering health care costs.

Ending the HIV Epidemic

Launched in 2020, the Ending the HIV Epidemic in the U.S. (EHE) initiative further expands federal efforts to reduce HIV transmission. For the RWHAP, the EHE initiative expands the program's ability to meet the needs of clients, specifically focusing on linking people with HIV who are either newly diagnosed, diagnosed but currently not in care, or are diagnosed and in care but not yet virally suppressed, to the essential HIV care, treatment, and support services needed to help them reach viral suppression.

Making America Healthy Again

The Ryan White HIV/AIDS Program helps advance the Making America Healthy Again (MAHA) priorities by:

- **Expanding access to primary care** for people with HIV, particularly those with low incomes, and by Strengthening the health workforce.
- **Fighting the chronic disease epidemic** by providing HIV medical care, treatment, and support services to people with HIV.
- **Supporting improved nutrition** by providing patient-centered focused medical nutrition therapy and food services.
- **Supporting disease prevention** through HIV care and treatment services that help people reach viral suppression, so they live longer, healthier lives and do not transmit HIV.

Key accomplishments

- **Nearly 602,000 people with HIV** in the U.S. received life-saving care, medication, and essential support services through the RWHAP, representing over half of all people diagnosed with HIV in the U.S. This is an increase of nearly 26,000 clients.
- **More than 91%** of Ryan White HIV/AIDS Program patients receiving HIV medical care were virally suppressed in 2024. This is up from 69.5% of patients virally suppressed in 2010 and significantly higher than the 67.2% virally suppressed nationally among all people with diagnosed HIV.
- **More than 47%** of Ryan White HIV/AIDS Program clients are aged 50 years and older, demonstrating the program's success in supporting older clients and its commitment to addressing the unique needs of people aging with HIV.

Program requirements and expectations

Your state/territory should conduct activities to provide core medical and/or support services, as defined in HAB Policy Clarification Notice (PCN) 16-02: RWHAP Services: Eligible Individuals and Allowable Uses of Funds. Your project should address unmet needs among HIV-positive people and improve client-level health outcomes across the HIV care continuum, including viral suppression.

Eligible RWHAP Part B states/territories that are focus areas, or have counties that are focus areas, for the Ending the HIV Epidemic in the U.S. (EHE) initiative should consider if they still need supplemental funding.

As required in section 2620(b) of the Public Health Service (PHS) Act, states/territories must demonstrate the severity of the need for RWHAP Part B supplemental funding, using quantifiable data in one or more of these areas:

- The unmet need for such services, as determined under section 2617(b) of the PHS Act.
- An increasing need for HIV/AIDS-related services, including relative rates of increase in the number of HIV/AIDS cases.

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- The relative rates of increase in the number of HIV/AIDS cases within subpopulations.
- The current prevalence of HIV/AIDS.
- Relevant factors related to the cost and complexity of delivering health care to individuals with HIV/AIDS in the eligible area.
- The impact of comorbid factors, including co-occurring conditions, determined relevant by the Secretary.
- The prevalence of homelessness.
- The prevalence of individuals who were released from federal, state, or local prisons during the past three years and had HIV/AIDS when they were released.
- Factors that limit access to health care, including geographic variation, adequacy of health insurance coverage, and language barriers.
- The impact of a decline in the amount of RWHAP Part B funding received on services available to all individuals with HIV/AIDS identified and eligible under this title.

Statutory authority

42 U.S.C. § 300ff-29a (Title XXVI, § 2620 of the Public Health Service Act)

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Award information

Funding policies and limitations

Changes in HHS regulations

As of October 1, 2025, HHS has adopted 2 CFR Part 200, with some modifications included in 2 CFR Part 300. These regulations replace those in 45 CFR Part 75.

Policies

- To make an award, funding must be available and allocated for this program and purpose, at which point we will move forward with the review and award process.
- Have clear policies and good financial practices to avoid spending HRSA funds on unallowable activities. Like other award rules, we may audit your policies, procedures, and controls.
- If we receive more funding for this program, we may:
  - Fund more applicants from the rank order list.
  - Extend the period of performance.
  - Award supplemental funding.

General limitations

- For guidance on some types of costs we do not allow or restrict, see:
  - Project Budget Information in the Application Guide [PDF].
  - 2 CFR Part 200 Subpart E — General Provisions for Selected Items of Cost.
  - Allowable and Unallowable Costs and Activities, in the HHS Grants Policy Statement.
- All costs must be reasonable, necessary, allocable to the award, and adequately documented (2 CFR 200.403).
- You cannot earn profit from the federal award. See 2 CFR § 200.400(g).
- Current appropriations law includes a salary limit of $228,000 as of January 2026 that applies to this program. You may pay salaries at a higher rate if the rate beyond the salary rate limit (Executive Level II) is paid with non-HHS funds. For help calculating salaries under this limit, read more at “salary rate limitation” in the application guide.

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Program-specific statutory or regulatory limitations

- Pursuant to section 2620(c) of the PHS Act, the Secretary prioritizes funds to states/territories to address the reduction or disruption of services due to a decline in the amount of formula funding. To determine whether funding has declined, we compare the amount of formula funding received in the current fiscal year (FY) to the amount received in FY 2006.
- If your state/territory has current or potential shortfalls in ADAP resources, you should prioritize using RWHAP Part B supplemental funds to augment ADAP resources if your state/territory has any of these conditions:
  - Existing or anticipated ADAP waiting list.
  - Capped enrollment.
  - Reductions in ADAP formulary.
  - Reduction in the percentage of federal poverty level (FPL) eligibility requirement.
  - Other ADAP restrictions within your state/territory.
- Payor of Last Resort: Charges that are billable to third party payers are unallowable. Third party payers include Medicaid, Children's Health Insurance Programs (CHIP), Medicare (including Medicare Part D), basic health plans, or private insurance, including those purchased through the Health Insurance Marketplace. The RWHAP is the payor of last resort, and recipients must vigorously pursue alternate sources of payments.
  - HRSA expects you to determine eligibility for all clients and to confirm eligibility on a timely basis (please see HAB PCN 21-02).
  - You must coordinate with third-party payers that are ultimately responsible for covering the cost of services provided to eligible or covered people.
- As outlined under applicable statutes, regulation, or policy, you cannot use funds under this notice for the following purposes:
  - Payment for any item or service to the extent that payment has been made, or reasonably can be expected to be made, with respect to that item or service, under any state compensation program, insurance policy, federal or state benefits program, or any entity that provides health services on a prepaid basis (except for a program administered by or providing the services of the Indian Health Service).
  - Cash payment to intended recipients of RWHAP services.
  - International travel.

- Construction (minor alterations and renovations to an existing facility to make it more suitable for the purposes of the award program are allowable with prior HRSA approval).
-
- Development of materials designed to directly promote or encourage intravenous drug use or sexual activity, whether homosexual or heterosexual.
- Pre-Exposure Prophylaxis (PrEP) medications and related medical services or Post-Exposure Prophylaxis (PEP). This is because a person using PrEP or PEP is not diagnosed with HIV and therefore is not eligible for RWHAP-funded medication.

See Manage Your Grant for other information on costs and financial management.

Indirect costs

Indirect costs are costs you charge across more than one project that cannot be easily separated by project. For example, this could include utilities for a building that supports multiple projects.

To charge indirect costs, you can select one of two methods:

Method 1 – Approved rate. You currently have an indirect cost rate approved by your cognizant federal agency at the time of award.

Method 2 – *De minimis* rate. Per 2 CFR § 200.414(f), if you don't have a current negotiated indirect cost rate, you may elect to charge a *de minimis* rate. If you choose this method, costs included in the indirect cost pool must not be charged as direct costs.

This rate is up to 15% of modified total direct costs (MTDC). See 2 CFR § 200.1 for the definition of MTDC. You can use this rate indefinitely for all your federal awards or until you choose to receive a negotiated rate.

Consider your indirect costs when developing your budget.

Program income

Program income is money earned as a result of your award-supported project activities. You must use any program income you generate from awarded funds for approved project-related activities. Find more about program income at 2 CFR 200.307.

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Step 2:
Get Ready to Apply

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Get registered

SAM.gov

You must have an active account with SAM.gov to apply. SAM.gov registration can take several weeks. Begin that process today.

To register:

- Go to SAM.gov Entity Registration and select Get Started. From the same page, you can also select the Entity Registration Checklist for the information you will need to register.
- You must agree to the financial assistance general certifications and representations [PDF] specifically. Those for contracts are different.

When you register, you will also receive your required Unique Entity Identifier (UEI).

Once you register:

- You will have to maintain your registration throughout the life of any award.
- If your organization has multiple UEIs, use the one associated with your physical location.

If you need additional information about user roles in SAM.gov, see “Get registered: SAM.gov user roles” in the application guide.

Grants.gov

You must also have an active account with Grants.gov. You can see step-by-step instructions at the Grants.gov Quick Start Guide for Applicants and How to Apply for Grants.

Find the application package

The application package has all the forms you need to apply. You can find it online. Go to Grants Search at Grants.gov and search for opportunity number HRSA-26-074.

After you select the opportunity, we recommend that you select the Subscribe button to get updates.

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Application writing help

Visit HHS Tips for Preparing Grant Proposals.

Visit HRSA's How to Prepare Your Application page for more guidance.

See Apply for a Grant for other help and resources.

Join the webinar

For more information about this opportunity, join the webinar: Webinar information will be posted to the Related Documents tab on Grants.gov. We recommend you "Subscribe" to the NOFO on Grants.gov to receive updates when documents are posted.

Have questions? Go to Contacts and Support.

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Step 3:
Build Your Application

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Application checklist

There are two types of forms in Grants.gov:

- Some forms allow you to upload components of your application to the form. These include components like your project narrative, budget and budget narrative, and attachments.
- Other forms are more typical, fill-in-the-blank forms.

Make sure that you have everything you need to apply.

Narratives

Component	Grants.gov form	Included in page limit*?
☐ Project narrative	Project Narrative Attachment form.	Yes
☐ Budget narrative	Budget Narrative Attachment form.	Yes

Attachments

Insert each in the Attachments Form in this order.

Component	Included in page limit*?
☐ 1. Staffing plan and job descriptions	Yes
☐ 2. Biographical sketches	No
☐ 3. Project organizational chart	Yes
☐ 4. Tables and charts	No
☐ 5. Core medical services waiver	No
☐ 6. Epidemiological data snapshot	Yes
☐ 7. Unmet need framework and narrative	No
☐ 8-15. Other relevant documents	Yes

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Other required forms

Upload using each required form in Grants.gov.

Component	Included in page limit*?
☐ Application for Federal Assistance (SF-424)	No
☐ Budget Information for Non-Construction Programs (SF-424A)	No
☐ Project Abstract Summary form	No
☐ Disclosure of Lobbying Activities (SF-LLL), optional	No
☐ Project/Performance Site Location(s)	No
☐ Grants.gov Lobbying form	No
☐ Key Contacts	No

*Only what you attach in these forms counts toward the page limit. The forms themselves do not count.

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Application contents and format

This section includes guidance on each component found in the application checklist.

Application page limit: 60

Submit your information in English and express whole number budget figures using U.S. dollars.

Required format

Required format for project summary, project narrative, budget narrative, and attachments:

Font: A readable font like Arial, Courier, CG Times, or Times New Roman.

File format: We only accept the following document formats:

- .PDF — Adobe Portable Document Format
- .DOC/.DOCX — Microsoft Word
- .RTF — Rich Text Format
- .TXT — Text
- .WPD — Word Perfect Document
- .XLS/.XLSX — Microsoft Excel
- .VSD — Microsoft Visio

Size: 12-point font
Footnotes, charts, graphics, and budget tables may be 10-point or higher.

Ink color: Black

Spacing: Single-spaced, including all text and tables.

Alignment: Left

Headings: Bold all headings and align left.

Size: 8.5 x 11 (Make sure the print area is set and allows printing to 8.5 x 11.)

Margins: 1-inch on all sides.

Footer: On each page as the footer, include your organization's name and page numbers. If a competing continuation or competing supplement, also include your 10-digit award number.

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Page numbering:

- Do not number the standard OMB-approved forms.
- Number each attachment page sequentially (that is, 1, 2, 3).
- Reset the numbering for each attachment.
- Treat each attachment as a separate section.

File names: You can find guidance for naming our files in the application guide.

Project narrative

Introduction

See merit review criterion 1: Need.

Briefly describe how you will use RWHAP Part B supplemental funding to support a comprehensive system of high-quality care and treatment for people with HIV.

- Describe how the comprehensive system of care and treatment will improve outcomes across the HIV care continuum.
- Provide a snapshot of epidemiological data as Attachment 6. Describe the current prevalence of HIV/AIDS in your state/territory using data tables or figures. The page limit is 4 pages.

Need

See merit review criterion 1: Need.

Need for HIV-related services, including augmenting ADAP

Explain why you need funds to address issues such as:

- Unmet need.
- An increased need due to an increase in relative rates or prevalence of HIV/AIDS cases.
- A decline in available funding for HIV services, including ADAP.

Note: If you are requesting funds specifically for unmet need, then you must submit an Unmet Need Framework and narrative as **Attachment 7**.

If you are using funds to augment ADAP services, include information on either of the following, if applicable, in a narrative format:

- An existing or anticipated ADAP waiting list.
- Other cost containment measures. These could include capped enrollment, reduction of ADAP formulary, or reduction in the percentage of FPL eligibility requirement.

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Assessment of increases in the number of cases of HIV/AIDS within new or emerging subpopulations

If you are requesting funding to address needs for new or emerging subpopulations with limited access to existing HIV/AIDS care and services, address all the following bullet points. Explain how you will use funds to meet the need. Select six or fewer subpopulations.

- Unique challenges for each subpopulation related to the service delivery system.
- Service gaps for each subpopulation.
- Estimated costs of care for delivering service to each subpopulation.
- Current HIV viral suppression for each subpopulation.

Impact of comorbidities and other factors on the cost and complexity of providing care

If you request funding to address the impact of comorbidities and other factors on the cost and complexity of providing care, include a table as **Attachment 4** that provides quantitative evidence addressing these impacts. Include data sources. In this section, you must include a narrative explaining the data you provided in the table as **Attachment 4**.

You only need to include information on comorbidities and other factors for which you are applying for funding. Where applicable, include the following information in the table:

- Rates of sexually transmitted infections (STIs), including syphilis.
- Rates of hepatitis and tuberculosis.
- Rates of substance use and mental health disorders.
- Estimated number of people who are homeless.
- Estimated number of people with HIV who were released from federal, state, or local correctional facilities (i.e., prisons and jails) in the past three (3) years.
- The number and percent of people without insurance coverage, including those without Medicaid.
- The number and percent of people with HIV living at or below 138% and 400% of the 2026 FPL. Also include information about your FPL requirements for RWHAP eligibility.

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Access to health care

You may use funds to improve access to HIV health care in your state/territory. This includes access based on either:

- Geographic variation.
- Lack of health insurance.

Discuss the factors impacting access to care. Describe how you will use the requested funds to address each factor.

Approach

See merit review criterion 2: Response.

Describe how you will do all the following to address your demonstrated needs:

- Use programmatic and fiscal forecasting tools to meet projected service needs.
- Develop, maintain, streamline, and/or diversify service delivery models, service contracts, strategic partnerships, and/or collaborations.
- Involve clients, families, and communities with and affected by HIV, as appropriate, in planning, implementing, and improving your project.

High-level work plan

See merit review criteria 2: Response and 4: Impact.

In a narrative format, describe the following.

- How funded services will be used for all the following:
  - Promoting access to high-quality HIV care.
  - Addressing gaps in services.
  - Maximizing health outcomes along the HIV care continuum.
- How you will conduct all these activities:
  - Working with internal and external stakeholders, including people with HIV, to plan program activities.
  - Using the HIV care continuum to respond to the needs of people with HIV.
  - Ensuring availability of the same services throughout your jurisdiction.

In a table or outline format, provide goals and objectives that are specific, measurable, achievable, realistic, and time-framed (SMART). Also address all of these:

- The relationship of the goals and objectives to the needs you will use the requested funds to address.
- The core medical and support services you will provide.

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- The HIV care continuum stages tied to the goals and objectives.
- The anticipated outcome measures.

Resolving challenges

See merit review criterion 2: Response.

Discuss any challenges you anticipate in planning and implementing the proposed project. Include all the following:

- Specific challenges related to each identified need area that you are requesting funding for. This could include access to health care or impact of comorbidities.
- Specific activities or strategies you will use to identify risks and mitigate or resolve these challenges.

Performance reporting and evaluation

See merit review criteria 3: Performance reporting and evaluation and 5: Resources and capabilities.

Discuss your evaluation process and describe all the following:

- How you will collect and analyze data and use it for continuous quality improvement.
- The specific staff who will implement your evaluation process for this project.
- The systems (such as software) and other resources that are available to support evaluation efforts.
- How you will share evaluation results internally and externally with key stakeholders, including people with HIV, to improve program implementation and outcomes.
- How you will determine whether the SMART objectives you proposed in your work plan have been achieved.

See the reporting section for more information.

Sustainability

See merit review criterion 4: Impact.

We expect you to sustain key project elements that improve practices and outcomes for the population of focus. Propose a plan to sustain your project after the period of federal funding ends.

- Describe the actions you'll take to obtain future sources of funding.
- Discuss challenges that you'll likely encounter in sustaining the program. Include how you will resolve these challenges.

Organizational Information

See merit review criterion 5: Resources and capabilities.

- Briefly describe your agency's mission and structure, including personnel and facilities.
- Describe the scope of your current RWHAP activities.
- Explain how your mission, structure, and scope of RWHAP activities will help you carry out the program requirements of this project.
- If you use funds for personnel costs, you must submit all the following as attachments:
  - A staffing plan and job description for key personnel as **Attachment 1**.
  - Biographical sketches of key personnel as **Attachment 2**.
  - A project organizational chart as **Attachment 3**.

Budget and budget narrative

See merit review criterion 6: Support requested.

Your **budget** should follow the instructions in budget narrative: detailed instructions section of the Application Guide and the instructions listed in this section. Your budget should show a well-organized plan.

HHS now uses the definitions for equipment and supply in 2 CFR 200.1. The new definitions change the threshold for equipment to the lesser of the recipient's capitalization level or $10,000 and the threshold for supplies to below that amount.

The total project or program costs are all allowable (direct and indirect) costs used for the HRSA award activity or project. This includes costs charged to the award and non-federal funds used to satisfy a matching or cost-sharing requirement (which may include maintenance of effort, if applicable).

The **budget narrative** supports the information you provide in Standard Form 424-A. It includes an itemized breakdown and a clear justification of the costs you request. The merit review committee reviews both.

As you develop your budget, consider:

- If the costs are reasonable, allowable and allocable, and consistent with your project's purpose and activities.
- The restrictions on spending funds. See funding policies and limitations.

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In addition, you must:

- Submit a separate line-item budget using Section B Object Class Categories of the SF-424A. The program budget categories for the line-item budget include:
  - **Administration:** Include all funds allocated to recipient administration, planning and evaluation, and clinical quality management.
  - **ADAP:** Include all funds allocated to ADAP activities.
  - **Consortia:** Include all funds allocated to consortia.
  - **Direct services:** Include all funds allocated to state direct services, home- and community-based care, and health insurance premium and cost-sharing assistance.
- Consider the following caps on expenses:
  - Administrative costs may not exceed 10% of the total grant award.
  - Planning and evaluation costs may not exceed 10% of the total grant award.
  - Together, administration and planning and evaluation may not exceed 15% of the total award. For further guidance on the treatment of costs under the 10% administrative limit, refer to HAB PCN 15-01 Treatment of Costs under the 10% Administrative Cap for Ryan White HIV/AIDS Program Part A, B, C, and D [PDF].
- Fulfill the Core Medical Services Requirement. RWHAP Part B supplemental funding is subject to Section 2612(b)(1) of the PHS Act. This act requires that after you have reserved funding for administration, planning and evaluation, and clinical quality management, you must use at least 75% of the remaining funds to provide core medical services that are needed in the state/territory for people with HIV who are eligible under RWHAP. The core medical and support service category definition for this award can be found in HRSA HAB Policy Clarification Notice (PCN) 16-02: RWHAP Services: Eligible Individuals and Allowable Use of Funds [PDF].
  - If you are seeking a waiver for this requirement, you must submit a waiver request. You can do this either before applying, with this application (as Attachment 5, Core Medical Services Waiver), or up to four months into the award period. Submission must be in accordance with HAB Policy Notice (PN) 21-01 Waiver of the RWHAP Core Medical Services Expenditures Requirement [PDF].

To create your budget narrative, see budget narrative detailed instructions in the Application Guide [PDF].

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Attachments

Place your attachments in this order in the Attachments Form. See application checklist to determine if they count toward the page limit.

Unless the instructions below require it, do not submit organizational brochures or other promotional materials (for example, slides, films, clips).

Attachment 1: Staffing plan and job descriptions

Provide a staffing plan and job descriptions for all key personnel included in the budget.

Limit each job description to one page. Include the role, responsibilities, and qualifications of the proposed project staff.

If your program will not use RWHAP Part B supplemental funding for staffing, attach a one-page document that says, “Attachment 1: Not Applicable.”

Attachment 2: Biographical sketches

Provide biographical sketches of all key personnel included in the budget.

If your program will **not** use RWHAP Part B supplemental funding for staffing, provide a one-page document that says, “Attachment 2: Not Applicable.”

Note: Each biographical sketch should be no more than two pages. Do not include non-public, personally identifiable information. If you include someone you have not hired yet, provide a letter of commitment from that person along with the biographical sketch.

Attachment 3: Project organizational chart

Provide a one-page project organizational chart highlighting the key personnel included in the budget.

If your program will **not** use RWHAP Part B supplemental funding for staffing, provide a one-page document that says, “Attachment 3: Not Applicable.”

Attachment 4: Tables and charts

Provide the cost and complexity comorbidities table and narrative. See the full description of the comorbidities table in the need section of the project narrative.

If your program will **not** use RWHAP Part B supplemental funding due to the impact of comorbidities in the state/territory, provide a one-page document that says, “Attachment 4: Not Applicable.”

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Attachment 5: Core medical services waiver (if applicable)

You may provide a Core Medical Services Waiver request and supporting documents as Attachment 5.

If you are **not** applying for a waiver now, provide a one-page document that says, “Attachment 5: Not Applicable.”

Attachment 6: Epidemiological data snapshot

This attachment is required for all applicants.

Page limit: 4 pages

Provide data tables or figures, as described in the introduction section of the project narrative, using the most recent available epidemiological data.

Attachment 7: Unmet need framework

If you are applying for RWHAP Part B supplemental funding due to unmet need, provide the Unmet Need Framework and narrative.

If your program will **not** use RWHAP Part B supplemental funding due to unmet need, provide a one-page document that says, “Attachment 7: Not Applicable.”

Attachment 8-15: Other relevant documents

Provide any other documents that are relevant to the application. If you include letters of support, they must be dated and indicate specific commitment to the project, like in-kind services, dollars, staff, space, or equipment.

If you do **not** have any other relevant documents, provide a one-page document that says, “Attachments 8-15: Not Applicable.”

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Other required forms

You will need to complete some other forms. Upload the following forms at Grants.gov. You can find them in the NOFO application package or review them and any available instructions at Grants.gov Forms.

Forms	Submission Requirement
Application for Federal Assistance (SF-424)	With application.
Project Abstract Summary form	With application.
Grants.gov Lobbying form	With application.
Project/Performance Site Location(s)	With application.
Budget Information for Non-Construction Programs (SF-424A)	With application.
Key Contacts	With application.

Form instructions

The application guide [PDF] has detailed instructions for:

- The Application for Federal Assistance (SF-424).
- The Budget Information for Non-Construction Programs (SF-424A).

Project abstract summary form instructions

Complete the information in the Project Abstract Summary form. Include a short description of your proposed project. Include the needs you plan to address, the proposed services, and the population groups you plan to serve. For more information, see Section 3.1.2 of the Application Guide [PDF].

In this section, also describe all the following:

- Why you need RWHAP Part B supplemental funding to ensure comprehensive HIV care and treatment for people with HIV in your state/territory.
- How this supplemental funding will improve viral suppression and improve client health outcomes across the HIV care continuum.
- The severity of the HIV epidemic in your state/territory, using quantifiable data on:
  - Epidemiology.
  - Comorbidities.
  - Cost of care.
  - Service needs of emerging subpopulations.

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- Unmet need for core medical services (as defined by HAB PCN 16-02 Ryan White HIV/AIDS Program Services: Eligible Individuals and Allowable Use of Funds [PDF]).
- Unique service delivery challenges.

Important: public information

When filling out your SF-424 form, pay attention to Box 15: Descriptive Title of Applicant's Project.

We share what you put there with USAspending. This is where the public goes to learn how the federal government spends their money.

Instead of just a title, insert a short description of your project and what it will do.

See instructions and examples [PDF].

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Step 4: Understand Review, Selection, and Award

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Application review

Initial review

We will review your application to make sure that it meets eligibility criteria, including the completeness and responsiveness criteria. If your application does not meet these criteria, we will not fund it. If this is the case, we will notify your authorized official.

We will not review any pages that exceed the page limit.

Merit review

A panel reviews all applications that pass the initial review. You can find more about the merit review process in the application guide. The members use these criteria.

Criterion	Total number of points = 100
1. Need	45 points
2. Response	20 points
3. Performance reporting and evaluation	10 points
4. Impact	10 points
5. Resources and capabilities	5 points
6. Support requested	10 points

Criterion 1: Need (45 points)

See the project narrative Introduction and Need sections.

The panel will review your application for how well it does the following.

- **Comprehensive system of care and treatment (10 points) —** Details how your state/territory will use RWHAP Part B supplemental funding to support a comprehensive system of high-quality care and treatment for people with HIV and improve outcomes across the HIV care continuum.
- **Data supporting need (15 points) —** Includes data that supports the described need.
- **Severity of need (20 points) —** Demonstrates need and the relative severity of that need for the areas for which you are requesting funding. This includes all the information requested in the need section of the project narrative and its subsections.

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Criterion 2: Response (20 points)

See the project narrative Approach, High-level work plan, and Resolving challenges sections.

The panel will review your application for how well it:

- Proposes strong, appropriate goals, objectives, outcome measures, and activities that relate well to the program's purpose.
- Shows how you will engage stakeholders, including people with HIV, in planning, implementing, and improving your project.
- Details challenges likely to be encountered, and how you will resolve them and address possible risks.

Criterion 3: Performance reporting and evaluation (10 points)

See the project narrative Performance reporting and evaluation section.

The panel will review your application for the following.

Evaluation

- The appropriateness of your methods to collect, analyze, and use data to develop and carry out the project.
- The effectiveness of available resources (such as staff or software) to carry out the evaluation.
- The suitability of plans to share project evaluation results with stakeholders, including people with HIV.

Performance measurement

- Evidence that the measures you selected will assess whether you have met project goals and objectives, and to what extent the results can be attributed to the project.

Criterion 4: Impact (10 points)

See the project narrative High-level work plan and Sustainability sections.

The panel will review your application for:

- How effective the proposed project is in potentially improving the stages of the HIV care continuum. This includes your goals, objectives, outcome measures, and activities.

- How strong the project is in addressing gaps in service. This includes addressing unmet needs due to lack of funds, improving health outcomes, reducing the number of people out of care, and working toward ending the HIV epidemic.
- The strength of the proposed plan to sustain key elements of the project beyond the performance period.

Criterion 5: Resources and capabilities (5 points)

See the project narrative Organizational information and Performance reporting and evaluation sections.

The panel will review your application to determine the extent to which:

- Your agency can fulfill the needs of the proposed project.
- The project staff funded by this award (if any) have the experience necessary to carry out the project.

Criterion 6: Support requested (10 points)

See the Budget and budget narrative section.

The panel will review your application to determine:

- How reasonable costs support the objectives described in the application.
- How reasonable costs are and how well they align with the project's scope.

We do not consider **voluntary** cost sharing during merit review.

We review your application based on its technical merit.

Risk review

Before making an award, we review your award history to assess risk. We need to ensure all prior awards were managed well and demonstrated sound business practices. We:

- Review any applicable past performance.
- Review audit reports and findings.
- Analyze the budget.
- Assess your management systems.
- Ensure you continue to be eligible.
- Make sure you comply with any public policies.

We may ask you to submit additional information.

As part of this review, we use SAM.gov Entity Information Responsibility/Qualification to check your history for all awards likely to be more than $250,000 over the period of

performance. You can comment on your organization's information in SAM.gov. We'll consider your comments before making a decision about your level of risk.

If we find a significant risk, we may choose not to fund your application or to place specific conditions on the award.

For more details, see 2 CFR 200.206.

Selection process

When making funding decisions, we consider:

- The amount of available funds.
- Assessed risk.
- Alignment with HRSA Mission and Strategic Priorities
- Merit review results. These are key in making decisions but are not the only factor.
- The larger portfolio of HRSA-funded projects, including project type and geographic distribution.
- The funding priorities, funding preferences, and special considerations listed.

You cannot appeal a denial, or the amount of funds awarded" which comes above funding priorities: "Additionally, we may not make an award if you are delinquent on two or more Single Audit Report.

Funding preferences

Priority funding

Qualifications to meet the funding preferences:

Qualification 1: RWHAP Part B base formula award decreased by greater than 10% between FY 2006 and FY 2026.

You can request funding preference if:

Section 2620(c) of the PHS Act directs the Secretary to provide funds to states/territories to address the decline or disruption of services related to the decline in the amount of formula funding. We set aside a portion of the RWHAP Part B supplemental funding to award priority funds in conformance with this statutory requirement.

You will be granted priority funding if your RWHAP Part B base formula award decreased by more than 10% between FY 2006 and FY 2026. If you are determined eligible for priority funding, we will calculate the additional amount to be awarded and include that amount in the final award.

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Award notices

We issue Notices of Award (NOA) on or around the start date listed in the NOFO. See How we make awards in the Application Guide [PDF] for more information.

By drawing down funds, you accept the terms and conditions of the award.

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Step 5:
Submit Your Application

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Application submission and deadlines

Your organization's authorized official must certify your application. See the section on finding the application package to make sure you have everything you need.

Application deadline

You must submit your application by Friday, July 10, 2026, at 11:59 p.m. ET.

Grants.gov creates a date and time record when it receives applications.

If you need a deadline extension, see "requesting a waiver" in the application guide.

Submission method

Grants.gov

You must submit your application through Grants.gov. You may do so using Grants.gov Workspace. This is the preferred method. For alternative online methods, see Applicant System-to-System.

For instructions on how to submit in Grants.gov, see the Quick Start Guide for Applicants. Make sure that your application passes the Grants.gov validation checks, or we may not get it. Do not encrypt, zip, or password protect any files.

If Grants.gov rejects your application due to errors, you must correct and resubmit before the deadline.

If you want to know more about correcting errors or tracking your application, you can refer to the application guide.

Have questions? Go to Contacts and Support.

Other submissions

Intergovernmental review

This NOFO is not subject to Executive Order 12372, Intergovernmental Review of Federal Programs. No action is needed.

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Step 6: Learn What Happens After Award

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Post-award requirements and administration

Administrative and national policy requirements

There are important rules you need to know if you get an award. You must follow:

- All terms and conditions in the Notice of Award (NOA). We incorporate this NOFO by reference.
- The regulations at 2 CFR Part 200, Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards, modifications at 2 CFR Part 300, and any superseding regulations.
- The HHS Grants Policy Statement. Your NOA will reference this document. If there are any exceptions to the GPS, they'll be listed in your NOA.
- All federal statutes and regulations relevant to federal financial assistance, including those highlighted in HHS Administrative and National Policy Requirements [PDF].
- The requirements for performance reporting and evaluation in 2 CFR 200.301.
- All anti-discrimination laws: By applying for or accepting federal funds from HHS, you certify compliance with all federal antidiscrimination laws and these requirements. Complying with those laws is a material condition of receiving federal funding streams. You are responsible for ensuring subrecipients, contractors, and partners also comply.

Required Alignment with Health Resources and Services Administration (HRSA) Mission and Strategic Priorities

Recipients must use funds awarded under this NOFO to implement program goals or agency priorities in accordance with the HRSA vision, mission, core values, and strategic priorities, where authorized by law.

In administering programs under this and all funding announcements, HRSA prioritizes:

- **Evidence-based healthcare:** Funding activities supported by rigorous scientific evidence, particularly for programs serving children and adolescents, where HRSA is committed to approaches that reflect the highest standards of clinical care and child safety.
- **Biological and physiological integrity:** Recognizing the relevance of biological sex to health outcomes, HRSA encourages applicants to account for sex-based health factors

in program design, data collection, and service delivery where scientifically appropriate.

HRSA will implement these priorities consistent with applicable laws, regulations, court orders, and all required administrative procedures. Applicants are encouraged to describe how their proposed programs align with these priorities in their project narratives.

Funded activities must advance HRSA's vision of protecting and improving the health and well-being of Americans. The particular focus is on those who are medically vulnerable or live in areas with limited access to care. HRSA's duty is to serve wisely, effectively, and with measurable results that justify every taxpayer dollar invested.

Consistent with HRSA's priorities, in carrying out any project funded under this NOFO, the recipient must adhere to the following principles, where they are consistent with the authority and scope of the award and its activities:

- **Gold standard science:** Design and deliver services using gold standard evidence-based and evidence-informed approaches, establish measurable performance goals, and use data to monitor outcomes and drive continuous improvement.
- **Program integrity and fiscal stewardship:** Recipients must:
    - Administer funds in accordance with all applicable federal statutes, regulations, and award conditions.
    - Maintain strong internal controls.
    - Prevent waste, fraud, and abuse.
- **Partnership and local leadership:** Coordinate with state, tribal, territorial, local, and community partners, as appropriate, and tailor services to meet community-identified needs while respecting local decision-making authority.

Recipients must manage any project awarded under this NOFO in accordance with the following objectives in programs authorized to advance them:

- **Make America Healthy Again (MAHA):** While ensuring access to high-quality, affordable physical and mental health care, HRSA prioritizes the health and well-being of all Americans by supporting common-sense, evidence-based health policies that promote:
    - Personal responsibility.
    - Strong families and communities.
    - Proper nutrition.
    - The prevention and management of chronic disease.
- **Child protections, biological integrity, parental rights, and lawful use of funds:** HRSA prioritizes safeguarding children's health and safety by:
    - Not supporting medical interventions for gender dysphoria in minors that lack a

strong evidence base.

- Applying sex-based definitions grounded in biological reality.
- Supporting parental authority, transparency, and choice in education, including school-based health centers that respect parental rights and religious upbringing.
- Ensuring taxpayer funds do not promote or support elective abortions, consistent with federal law and the Hyde Amendment.

- **Advancing evidence-based, merit-driven, and ethically grounded health care**: HRSA will prioritize unbiased, transparent science; merit-based workforce opportunities; and programs that demonstrate measurable outcomes. HRSA will deprioritize organizations with:
  - Conflicts of interest.
  - "Harm reduction" models.
  - Housing-first approaches.
  - Activities that facilitate illegal drug use or unsafe medical practices.
- **Promoting public safety, lawful use of federal funds, and national health priorities:** To the extent permitted by law, HRSA will align funding with administration priorities by:
  - Supporting ending the HIV epidemic through authorized, evidence-based care.
  - Reserving benefits for eligible individuals.
  - Discouraging illegal immigration and unsafe community practices.
  - Prioritizing recipients that enforce public safety, address serious mental illness and substance use through treatment and recovery, and reduce homelessness responsibly.

To the extent allowable by law, under awards, HRSA will give priority to states and municipalities for programs to:

- Enforce prohibitions on open illicit drug use.
- Enforce prohibitions on urban camping and loitering.
- Enforce prohibitions on urban squatting.
- Enforce, and where necessary, adopt, standards that address individuals who are a danger to themselves or others and suffer from serious mental illness or substance use disorder, or who are living on the streets and cannot care for themselves. The approach must be through assisted outpatient treatment or by moving them into treatment centers or other appropriate facilities through civil commitment or other available means, to the maximum extent permitted by law.

HRSA will implement these priorities consistent with applicable laws, regulations, court orders, and any required procedures.

The recipient must demonstrate ongoing compliance with these priorities, in all programs that are authorized to advance them, through program design, implementation, reporting, and evaluation.

Failure to meaningfully align funded activities with the applicable requirements may result in corrective action, additional reporting requirements, or other actions consistent with federal grant regulations at 2 CFR. part 200 and the terms and conditions of this award. This includes termination under CFR. 200.340(a)(4) if an award no longer effectuates the program goals or agency priorities.

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Cybersecurity

- If awarded, you must develop plans and procedures, modeled after the NIST Cybersecurity framework, to protect HHS systems and data.

Successful applicants under this NOFO agree that:

Where award funding involves:	Recipients and subrecipients are required to:
Implementing, acquiring, or upgrading health IT for activities funded by any entity.	Use health IT that meets standards and implementation specifications adopted in 45 CFR 170, Subpart B, if such standards and implementation specifications can support the activity. Visit 45 CFR 170, Subpart B to learn more.
Implementing, acquiring, or upgrading health IT for activities by eligible clinicians in ambulatory settings, or hospitals, eligible under Sections 4101, 4102, and 4201 of the HITECH Act.	Use health IT certified under the ONC Health IT Certification Program if certified technology can support the activity. Visit Certification of Health IT to learn more.

If standards and implementation specifications adopted in 45 CFR part 170, Subpart B cannot support the activity, recipients and subrecipients are encouraged to use health IT that meets non-proprietary standards and implementation specifications developed by consensus-based standards development organizations. This may include standards identified in the ONC Interoperability Standards Advisory.

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Reporting

If you are funded, you will have to follow the reporting requirements in the reporting section of the Application Guide [PDF]. The NOA will provide specific details.

You must also follow these program-specific reporting requirements:

- Progress reports at the end of the period of performance.
- Annual performance reports.
- NOFO-specific reporting requirements:
  - **Federal Financial Report (SF-425).** You must account for your expenditures under the project for the year. We will provide more specific information in the notice of award (NoA). You can also see Reporting Requirements on HRSA's website.
  - **Program Terms Report (PTR).** You must submit a program terms report, which will be described in the NoA.
  - **RWHAP Services Report (RSR).** You must comply with the RSR data requirements and make sure your subrecipients also comply. The RSR captures information to show program performance and accountability.
    - All RWHAP core medical service and support service providers must submit client-level data, as instructed in the RSR manual.
    - We will provide further information in the NoA. You can also refer to the HIV/AIDS Program Client-Level Data website for additional information.
  - **ADAP Data Report (ADR).** If you spend any of the RWHAP Part B supplemental award on ADAP, you must comply with ADR data reporting requirements. You must also make sure your subrecipients comply. We will provide further information in the NoA. You can also refer to the HIV/AIDS Program ADAP Data Report website for additional information.

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Contacts and Support

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Agency contacts

Program and eligibility

Kibibi Matthews-Brown
Senior Program Advisor
Attn: Division of State HIV/AIDS Programs (DSHAP)
Ryan White HIV/AIDs Program Part B States/Territories Supplemental Grant Program
Health Resources and Services Administration
KMatthews-Brown@hrsa.gov
301-443-1035

Financial and budget

Olusola Dada
Grants Management Specialist
Division of Grants Management Operations
Office of Financial Assistance and Acquisition Management (OFAAM)
Health Resources and Services Administration
ODada@hrsa.gov
301-443-0195

HRSA Contact Center

Open Monday – Friday, 7 a.m. – 8 p.m. ET, except for federal holidays.
Call: 877-464-4772 / 877-Go4-HRSA
TTY: 877-897-9910

Electronic Handbooks Contact Center

Help with systems

Grants.gov

Grants.gov provides 24/7 support. You can call 800-518-4726, search the Grants.gov Knowledge Base, or email Grants.gov for support. Hold on to your ticket number.

SAM.gov

If you need help, you can call 866-606-8220 or live chat with the Federal Service Desk.

Helpful websites

- Application Guide [PDF]
- HRSA Grants page
- HHS Tips for Preparing Grant Proposals
- Grants.gov Frequently Asked Questions
- Grants.gov Applicant Training

EXHIBIT C

Notice of Funding Opportunity

Application due 07/08/2026

HRSA
Health Resources & Services Administration

HIV/AIDS Bureau

Ryan White HIV/AIDS Program Part C Capacity Development Program

Opportunity number: HRSA-26-061

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Before you begin

If you believe you are a good candidate for this funding opportunity, secure your SAM.gov and Grants.gov registrations now. If you are already registered, make sure your registrations are active and up-to-date.

SAM.gov registration (this can take several weeks)

You must have an active account with SAM.gov. This includes having a Unique Entity Identifier (UEI).

See Step 2: Get Ready to Apply

Grants.gov registration (this can take several days)

You must have an active Grants.gov registration. Doing so requires a Login.gov registration as well.

See Step 2: Get Ready to Apply

Apply by the application due date

Applications are due by 11:59 p.m. Eastern Time on 07/08/2026.

To help you find what you need, this NOFO uses internal links. In Adobe Reader, you can go back to where you were by pressing Alt + Left Arrow (Windows) or Command + Left Arrow (Mac) on your keyboard.

All activities proposed in your application and budget narrative must align with applicable law, including but not limited to statutes, executive orders, federal regulations and applicable judicial holdings. Accordingly, discretionary awards shall not be used to fund, promote, encourage, subsidize, or facilitate racial preferences or other forms of racial discrimination by the recipient, including activities where race or intentional proxies for race will be used as a selection criterion for employment or program participation; denial by the recipient of the sex binary in humans, or the belief that sex is a chosen or mutable characteristic; illegal immigration; or any other initiatives that compromise public safety. If an application does not align, the application will not receive funding to the extent permitted by law and applicable court orders.

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Step 1:
Review the Opportunity

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Basic information

Health Resources Services Administration

HIV/AIDS Bureau

Strengthening the capacity of community-based organizations to improve health outcomes and reduce HIV transmission, especially for people not yet in regular HIV care.

Summary

The Ryan White HIV/AIDS Program (RWHAP) provides a comprehensive system of HIV care that improves health outcomes and supports HIV viral suppression.

The purpose of the RWHAP Part C Capacity Development Program is to strengthen the capacity of community-based organizations to improve health outcomes and reduce HIV transmission, especially for people not yet in regular HIV care. The focus of this Part C program is on infrastructure.

This capacity development funding offers a one-year opportunity to carry out one short-term activity in FY 2026.

Funding details

Application types: New

Expected total available funding in FY26: $9,000,000

Expected number and type of awards: 60 G (Grants)

Funding range per award: Up to $150,000

We plan to fund awards in one 12-month budget period for a total one-year period of performance from 09/01/2026 to 08/31/2027.

The program and awards depend on the appropriation of funds and are subject to change based on the availability and amount of appropriations.

Have questions?
Go to Contacts and Support.

Key facts

Opportunity name:
Ryan White HIV/AIDS Program Part C Capacity Development Program

Opportunity number:
HRSA-26-061

Announcement version:
Initial

Federal assistance listing:
93.918

Key dates

NOFO issue date:

06/05/2026

Informational webinar:
See Join the webinar

Application deadline:
07/08/2026

Expected award date is by:
09/01/2026

Expected start date:
09/01/2026

See other submissions for other time frames that may apply to this NOFO.

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Eligibility

You can apply if your organization is in the United States.

Types of eligible organizations

These types of domestic organizations may apply:

- State governments.
- County governments.
- City or township governments.
- Special district governments.
- Public and State controlled institutions of higher education.
- Native American tribal governments (Federally recognized).
- Native American tribal organizations (other than Federally recognized tribal governments).
- Nonprofits having a 501(c)(3) status with the IRS, other than institutions of higher education.
- Nonprofits without 501(c)(3) status with the IRS, other than institutions of higher education.
- Private institutions of higher education.

Additional information on eligibility

Individuals are not eligible applicants under this NOFO.

Completeness and responsiveness criteria

We will review your application to make sure it meets these basic requirements to move forward in the competition.

We will not consider an application that:

- Is from an organization that does not meet all eligibility criteria.
- Requests funding above the award ceiling shown in the funding range.
- Is submitted after the deadline.
- Does not propose one of the three activities listed as described in the Program Requirements and Expectations section. The three available activities in this announcement are: 1. Electronic Health Record and Data Integration, 2. Telehealth, or 3. Office dental equipment for expanding service capacity.

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Application limits

You may not submit more than one application. If you submit more than one application, we will only accept the last on-time submission.

Cost sharing

This program has no cost-sharing requirement. If you choose to share in the costs of the project, we will not consider it during merit review. Recipients agree that once committed, cost sharing amounts are enforceable and subject to reporting and auditing requirements under 2 CFR 200.

Post-award requirements

Before you apply, make sure you understand the requirements that come with an award.

See Step 6: Learn What Happens After Award for information on regulations that apply, reporting, and more.

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Program description

Purpose

This one-year capacity development funding opportunity is intended to strengthen organizational capacity to develop, enhance, or expand access to high quality HIV care and treatment for low-income people with HIV, especially for people not yet in regular HIV care.

HRSA intends to fund one short-term activity under this program that can be completed by the end of the one-year period of performance.

Goal alignment

Proposed projects must:

- Align with program goals.
- Address unmet needs or gaps in care for people with HIV.
- Establish activities that represent a meaningful addition to your existing program.
- Support improved health outcomes for people with HIV.

For additional information, please refer to Policy Clarification Notice (PCN) 16-02 for a list of RWHAP allowable services and use of funds.

For more details, see Program requirements and expectations.

Background

The Ryan White HIV/AIDS Program

The Ryan White HIV/AIDS Program (RWHAP) has five statutorily defined Parts that provide grants to states, cities, counties, local clinics, and community-based organizations. The grants fund medical care, medication, and essential support services, to meet the needs of people with HIV and family members affected by HIV. Together these grants provide a comprehensive system of care to ensure low-income people with HIV have access to services for early diagnosis of HIV, linkage to care, medically appropriate treatment, retention in care, and sustained viral suppression (a very low or undetectable amount of HIV in the blood).

For nearly four decades, the RWHAP has funded services to provide HIV primary health care, medication, and essential support services, including mental health care, transportation, case management, nutrition, and housing. These services support

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clients to enter and remain in care, access medications, and reach viral suppression, reducing transmission and lowering health care costs.

Ending the HIV Epidemic

Launched in 2020, the Ending the HIV Epidemic in the U.S. (EHE) initiative further expands federal efforts to reduce HIV transmission. For the RWHAP, the EHE initiative expands the program's ability to meet the needs of clients, specifically focusing on linking people with HIV who are either newly diagnosed, diagnosed but currently not in care, or are diagnosed and in care but not yet virally suppressed, to the essential HIV care, treatment, and support services needed to help them reach viral suppression.

Making America Healthy Again

The Ryan White HIV/AIDS Program helps advance the Making America Healthy Again (MAHA) priorities by:

- **Expanding access to primary care** for people with HIV, particularly those with low incomes, and by strengthening the health workforce.
- **Fighting the chronic disease epidemic** by providing HIV medical care, treatment, and support services to people with HIV.
- **Supporting improved nutrition** by providing patient-centered focused medical nutrition therapy and food services.
- **Supporting disease prevention** through HIV care and treatment services that help people reach viral suppression so they live longer, healthier lives and do not transmit HIV.

Key accomplishments

- **Nearly 602,000 people with HIV** in the U.S. received life-saving care, medication, and essential support services through the RWHAP, representing over half of all diagnosed with HIV in the U.S. This is an increase of nearly 26,000 clients.
- **More than 91%** of Ryan White HIV/AIDS Program patients receiving HIV medical care were virally suppressed in 2024. This is up from 69.5% of patients virally suppressed in 2010 and significantly higher than the 67.2% virally suppressed nationally among all people with diagnosed HIV.
- **More than 47%** of Ryan White HIV/AIDS Program clients are aged 50 years and older, demonstrating the program's success in supporting older clients and its commitment to addressing the unique needs of people aging with HIV.

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Program requirements and expectations

You must show:

- That the proposed activity will strengthen organizational capacity.
- Your organization's intent and ability to maintain services, activities or equipment that were either purchased by, or are a direct result of, this federal award.
- Coordinating with other relevant HHS and HRSA providers to avoid duplicating efforts.

You must select only one activity.

You may submit a proposal for only **one** activity from the list of activities below. Do not submit a proposal that includes more than one activity.

The goal of these activities is to enhance an organization's infrastructure to better serve people with HIV.

- **Activity 1:** Electronic Health Record and Data Coordination
- **Activity 2:** Telehealth
- **Activity 3:** Dental equipment for expanding dental service capacity

Brief summaries of each activity

Activity 1: Electronic Health Record and Data Coordination

Improving how Electronic Health Records (EHR) connect with HIV data systems helps reduce duplicate data entry, increases the accuracy of data collection and reporting, and improves care coordination and tracking of referrals.

If you select this activity, funding may be used to purchase software to interface CAREWare (or other HIV data collection systems) with an existing EHR system.

Activities can include:

- Improving the accuracy and efficiency of data collection.
- Creating workflows to reduce administrative burden.
- Verifying and cleaning data.
- Testing historical and new data.
- Integrating oral health and primary care EHR systems.
- Securing consultant services for system integration and coordination.
- Enhancing interoperability to streamline RWHAP eligibility across Parts using existing data sources (e.g., Medicaid, health information exchanges, or marketplace records).

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All activities must be used to enhance or expand an existing EHR system to improve the:

- Quality.
- Pharmacological safety.
- Efficiency.

Funds cannot be used to purchase a brand-new EHR system. Any component purchased with federal funds must meet certification requirements set by the Assistant Secretary for Technology Policy and be configured to report clinical data electronically for HRSA reporting. More information is available at HealthIT.gov.

Activity 2: Telehealth

Telehealth improves access to care. It does this by reducing or eliminating the time needed to travel to and from appointments, and by lessening other social barriers such as caregiving responsibilities and lack of transportation that can cause people to miss their appointments.

Telehealth allows care delivery across any distance, expanding access to quality primary health.

If you select this activity, you must develop and acquire, through lease or purchase:

- Computer hardware and software.
- Audio and video equipment.
- Computer network equipment.
- Interactive equipment.
- Data terminal equipment.
- Other equipment that furthers the objectives of the proposed telehealth activity.

You must describe technology requirements and each type of equipment to be employed.

Include a concise description of the equipment's:

- Relevance to the project.
- Cost-effectiveness.
- Timeliness.
- Accuracy of care.
- Ease of use.

Discuss the telehealth reimbursement environment and whether Medicare, Medicaid, or private insurance in your state(s) cover telehealth services.

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For resources addressing this topic, access HRSA's Office for the Advancement of Telehealth and HHS's Telehealth for providers.

Activity 3: Dental Equipment for Expanding Dental Service Capacity

Personnel salaries for the provision of dental care (positions such as hygienist, dental assistant, dentist, etc.), purchase of a mobile unit, or construction are **not** allowable under this activity.

Oral health care is one of the core medical service categories in the RWHAP and can be a part of all clinical care plans for people with HIV. A large proportion of people with HIV have unmet dental care needs due to lack of available dental providers, limited transportation, costs of care, or other barriers.

RWHAP Part C supports a comprehensive approach to oral health care for low-income people with HIV, including the co-location of oral health care services with outpatient ambulatory health care.

If you select this activity, you must purchase dental equipment for the purpose of developing, enhancing, or expanding oral health care services for people with HIV.

Specifically, this activity involves creating or expanding a dental operatory in a clinic or in a mobile unit (e.g., van) through purchasing equipment such as:

- Dental patient chairs.
- Sterilization units.
- X-ray imaging instruments.
- Dental operating lights.
- Operatory cabinets.
- Hand pieces.

Statutory authority

42 U.S.C. §§ 300ff-54(c)(1)(B) and (Title XXVI, §§ 2654(c)(1(B) and 2693 of the Public Health Service Act).

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Award information

Funding policies and limitations

Changes in HHS regulations

As of October 1, 2025, HHS has adopted 2 CFR Part 200, with some modifications included in 2 CFR Part 300. These regulations replace those in 45 CFR Part 75.

Policies

- To make an award, funding must be available and allocated for this program and purpose, at which point we will move forward with the review and award process.
- Have clear policies and good financial practices to avoid spending HRSA funds on unallowable activities.
- Like other award rules, we may audit your policies, procedures, and controls.
- If we receive more funding for this program, we may:
  - Fund more applicants from the rank order list.
  - Extend the period of performance.
  - Award supplemental funding.

General limitations

- For guidance on some types of costs we do not allow or restrict, see
  - Project Budget Information in Section 3.1. of the Two-Tier Application Guide [PDF].
  - 2 CFR Part 200 Subpart E - General Provisions for Selected Items of Cost.
  - Allowable and Unallowable Costs and Activities, in the HHS Grants Policy Statement.
- All costs must be reasonable, necessary, allocable to the award, and adequately documented (2 CFR 200.403).
- You cannot earn profit from the federal award. See 2 CFR § 200.400(g).
- Current appropriations law includes a salary limit of $228,000 as of January 2026 that applies to this program. You may pay salaries at a higher rate if the rate beyond the salary rate limit (Executive Level II) is paid with non-HHS funds. For help calculating salaries under this limit, read more at “salary rate limitation” in the Two-Tier Application Guide [PDF].

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Program-specific statutory or regulatory limitations

You cannot use funds under this notice for the following:

- Funding restrictions included in Policy Clarification Notice 16-02 *Ryan White HIV/AIDS Program Services: Eligible Individuals and Allowable Uses of Funds*.
- Charges that are billable to third party payors (e.g., private health insurance, prepaid health plans, Medicaid, Medicare, Department of Housing and Urban Development (HUD) funding for housing services, other RWHAP funding including AIDS Drug Assistance Program).
- To directly provide housing or health care services (e.g., HIV care, counseling and testing) that duplicate existing services.
- Payments for clinical research.
- Payments for nursing home care.
- Cash payments to intended clients of RWHAP services.
- Purchase or improvement to land.
- Purchase, construction, or major alterations or renovations on any building or other facility (see 2 CFR 200 – subpart A Definitions).
- PrEP or non-occupational Post-Exposure Prophylaxis (nPEP) medications or the related medical services. As outlined in the updated November 16, 2021 RWHAP and PrEP program letter.
- Purchase of sterile needles and syringes for the purpose of hypodermic injection of any illegal drug use. Some aspects of syringe services programs are allowable with HRSA's prior approval and in compliance with HHS and HRSA policy. See Syringe Services Programs.
- Development of materials designed to directly promote or encourage intravenous drug use or sexual activity, whether homosexual or heterosexual.
- Research.
- Foreign travel.
- Long-term activities.
    - Instead, the activities should be short-term in nature with a targeted completion by the end of the one-year period of performance.

You must have policies, procedures, and financial controls in place. Anyone who receives federal funding must comply with legal requirements and restrictions, including those that limit specific uses of funding.

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Follow the list of statutory restrictions on the use of funds in Section 4.1 (Funding Restrictions) of the Application Guide. We may audit the effectiveness of these policies, procedures, and controls. 2 CFR § 200.216 prohibits certain telecommunications and video surveillance services or equipment. For details, see the HRSA Grants Policy Bulletin Number: 2021-01E.

See Manage Your Grant for other information on costs and financial management.

Indirect costs

Indirect costs are costs you charge across more than one project that cannot be easily separated by project. For example, this could include utilities for a building that supports multiple projects.

To incur indirect costs, you can select one of two methods:

Method 1 – Approved rate. You currently have an indirect cost rate approved by your cognizant federal agency at the time of award.

Method 2 – *De minimis* rate. Per 2 CFR § 200.414(f), if you do not have a current negotiated indirect cost rate, you may elect to charge a *de minimis* rate. If you choose this method, costs included in the indirect cost pool must not be charged as direct costs.

This rate is up to 15% of modified total direct costs (MTDC). See 2 CFR § 200.1 for the definition of MTDC. You can use this rate indefinitely for all your federal awards or until you choose to receive a negotiated rate.

Consider your indirect costs when developing your budget.

Program income

Program income is money earned as a result of your award-supported project activities. You must use any program income you generate from awarded funds for approved project-related activities. Find more about program income at 2 CFR 200.307.

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Step 2:
Get Ready to Apply

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Get registered

SAM.gov

You must have an active account with SAM.gov to apply. SAM.gov registration can take several weeks. Begin that process today.

To register:

- Go to SAM.gov Entity Registration and select Get Started. From the same page, you can also select the Entity Registration Checklist for the information you will need to register.
- You must agree to the financial assistance general certifications and representations specifically. Those for contracts are different.

When you register, you will also receive your required Unique Entity Identifier (UEI).

Once you register:

- You will have to maintain your registration throughout the life of any award.
- If your organization has multiple UEIs, use the one associated with your physical location.

If you need additional information about user roles in SAM.gov, see “Get registered: SAM.gov user roles” in the Application Guide [PDF].

Grants.gov

You must also have an active account with Grants.gov. You can see step-by-step instructions at the Grants.gov Quick Start Guide for Applicants and How to Apply for Grants.

Find the application package

The application package has all the forms you need to apply. You can find it online. Go to Grants Search at Grants.gov and search for opportunity number HRSA-26-061.

After you select the opportunity, we recommend that you click the Subscribe button to get updates.

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Application writing help

Visit HHS Tips for Preparing Grant Proposals.

Visit HRSA's How to Prepare Your Application page for more guidance.

See Apply for a Grant for other help and resources.

FAQs will be posted on our TA webpage after the webinar.

Join the webinar

Webinar information will be posted to the Related Documents tab on Grants.gov. We recommend you "Subscribe" to the NOFO on Grants.gov to receive updates when documents are posted.

Have questions? Go to Contacts and Support.

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Step 3:
Build Your Application

In this step

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Application checklist

There are two types of forms in Grants.gov.

- Some forms allow you to upload components of your application to the form. These include components like your project narrative, budget and budget narrative, and attachments, as applicable.
- Other forms are more typical, fill-in-the-blank forms.

Make sure that you have everything you need to apply.

Narratives

Component	Grants.gov form	Included in page limit*?
☐ **Project narrative**	Project Narrative Attachment form.	Yes
☐ **Budget narrative**	Budget Narrative Attachment form.	Yes

Attachments

Insert each in the Attachments Form in this order.

Component	Included in page limit*?
☐ 1. Proof of non-profit status	No
☐ 2. Funding preference	No
☐ 3. Federally negotiated indirect cost rate	No
☐ 4. Biographical sketches	No
☐ 5. Program specific line-item budget	Yes
☐ 6. Work plan	Yes
☐ 7. Staffing plan job descriptions	Yes
☐ 8. Agreements with other entities and memoranda of understanding	Yes
☐ 9-15. Other relevant documents	Yes

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Other required forms

Upload using each required form in Grants.gov.

Forms	Submission requirement
Application for Federal Assistance (SF-424)	With application.
Project Abstract Summary form	With application.
Grants.gov Lobbying form	With application.

*Only what you attach in these forms counts toward the page limit. The forms themselves do not count.

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Application contents and format

This section includes guidance on each component found in the application checklist.

Application page limit: 25

Submit your information in English and express whole number budget figures using U.S. dollars.

Required format

Required format for project summary, project narrative, budget narrative, and attachments.

Font: A readable font like Arial, Courier, CG Times, or Times New Roman

File format: We only accept the following document formats:

- .PDF - Adobe Portable Document Format
- .DOC/.DOCX - Microsoft Word
- .RTF - Rich Text Format
- .TXT - Text
- .WPD - Word Perfect Document
- .XLS/.XLSX - Microsoft Excel
- .VSD - Microsoft Visio

Size: 12-point font
Footnotes, charts, graphics, and budget tables may be 10-point or higher.

Ink color: Black

Spacing: Single-spaced, including all text and tables.

Alignment: Left

Headings: Bold all headings and align left.

Size: 8.5 x 11 (Make sure the print area is set and allows printing to 8.5 x 11.)

Margins: 1-inch on all sides

Footer: On each page as the footer, include your organization's name and page numbers. If a competing continuation or competing supplement, also include your 10-digit award number.

Page numbering:

- Do not number the standard OMB-approved forms.
- Number each attachment page sequentially (that is, 1, 2, 3).
- Reset the numbering for each attachment.
- Treat each attachment as a separate section.

File names: You can find guidance for naming your files in the Application Guide [PDF].

Project narrative

Introduction

See merit review criterion 1: Need

- Indicate the **one activity** you will implement:
  - Electronic Health Record and Data Coordination.
  - Telehealth.
  - Dental equipment for expanding office capacity.
- Describe the need for capacity development funding within your community and organization.
- Explain how the proposed activity will improve access to high-quality, HIV primary care for low-income people with HIV.
- Demonstrate how this is a **brand-new activity** and does not duplicate nor repeat any infrastructure development activities previously funded under the RWHAP Part C Capacity Development program.
- It also cannot duplicate activities of the RWHAP Part D Women, Infants, Children and Youth (WICY) Supplemental program (HRSA-24-061; HRSA-24-062) or FY 2025 (HRSA-25-050; HRSA-25-049).

Need

See merit review criterion 1: Need

For your proposed activity:

- Outline the equipment or data system needs you plan to address.
  - Describe the gaps in organizational capacity due to limitations in the current system infrastructure.
  - Include changes you have made to the current service delivery system.
  - Describe how the lessons you have learned will be applied to this activity.

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- Provide information specific to the selected activity and describe how these gaps or limitations are affecting the optimal provision of quality HIV primary care services.
    - Include how health care gaps or limitations are affecting your organization's ability to optimize HIV outcomes.
- Discuss the relevant barriers to successfully carry out the project. Include the steps you will take to minimize or overcome them.

Approach

See merit review criterion 2: Response

- Provide a clear description of the approach.
    - Include specific action steps.
    - Describe how actions will address the need and attain project objectives.
    - Include how the activity will be used to expand or improve client care.
    - Include the person(s) responsible for putting your proposed project in place (both staff and partners).
- Describe plans to share any information or products developed with the people and communities disproportionately impacted by HIV.
    - You should also plan to share lesson learned with these people and communities.
    - This should include community providers and project partners so they are made aware of the additional capability created by this proposed project.

Work plan

See merit review criteria 2: Response

Provide a detailed work plan for the 12-month period of performance of September 1, 2026 to August 31, 2027. For all activities, the work plan must:

- Describe the activity's goal and objectives.
- Describe how you'll achieve each of the objectives during the period of performance.
- List the key action steps needed to reach the goal.
    - Include when each step will be completed and who is responsible for each.
- Provide a timeline showing when each step will be completed and name the staff responsible for each step.
- Identify the measures you will use to evaluate success.
- Describe the expected outcomes that will show the impact of the activity.

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    - Outcomes may include changes in quality of service, service delivery type, treatment outcomes, knowledge, skills, practices, or other improvements.

Provide the above information in a table format with the following sections outlined:

- Goal and objectives.
- Action steps.
- Timeline.
- Person responsible.
- Evaluation measures.
- Outcomes.

You will also include a more detailed work plan that you will submit as Attachment 6.

Resolving challenges

See merit review criterion 4: Impact

- Discuss challenges that you are likely to encounter in your work plan and explain approaches that you'll use to resolve them.
- Describe the specific activities or strategies you will use to mitigate or resolve anticipated challenges. Include your plan to overcome any barriers to full implementation

Performance reporting and evaluation

See merit review criteria 3: Performance reporting and evaluation and 5: Resources and capabilities

Performance measurement and reporting

- Describe how you will collect and manage data in a way that helps you improve the way you carry out your activity.
- Track the goals and objectives identified in the work plan.

Program evaluation

- Describe how you will evaluate the effectiveness of your proposed capacity development project.
- Describe how you will share evaluation results internally with program staff and externally with key stakeholders (including people with HIV).

See the reporting section for more information.

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Sustainability

See merit review criterion 4: Impact

- Show that the activities outlined in the work plan can be reasonably completed within 12 months.
- Describe the organizational resources that you will use to sustain, without additional funds from the federal government, the project activities or enhancements supported by this award beyond the one-year period of performance.

Organizational information

See merit review criterion 5: Resources and capabilities

- Briefly describe the organizational skills, capabilities, and resources, including staff that will contribute to your organization's ability to carry out the proposed activity.
- Highlight key staff with relevant expertise and experience with similar work.
  - This information should align with the staffing plan provided in Attachment 7 and the biographical sketches of key personnel provided in Attachment 4.
- Discuss the organization's ability to secure agreements or contracts with community-based organizations, health care providers, and consultant services to achieve this project.
- Describe your plan to purchase equipment and execute contracts for services for this project within a reasonable timeframe.

Budget and budget narrative

See merit review criterion 6: Support requested

Your **budget** should follow the instructions in budget narrative: detailed instructions section of the Application Guide [PDF] and the instructions listed in this section. Your budget should show a well-organized plan.

HHS now uses the definitions for equipment and supply in 2 CFR 200.1. The new definitions change the threshold for equipment to the lesser of the recipient's capitalization level or $10,000 and the threshold for supplies to below that amount.

The total project or program costs are all allowable (direct and indirect) costs used for the HRSA award activity or project. This includes costs charged to the award and non-federal funds used to satisfy a matching or cost-sharing requirement (which may include maintenance of effort, if applicable).

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The **budget narrative** supports the information you provide in Standard Form 424-A. It includes an itemized breakdown and a clear justification of the costs you request. The merit review committee reviews both.

As you develop your budget, consider:

- If the costs are reasonable, allowable and allocable, and consistent with your project's purpose and activities.
- The restrictions on spending funds. See funding policies and limitations.

Line-Item budget:

- In addition to the SF-424 Application Guide requirements, you must also provide the line-item budget and budget narrative according to each object class category (e.g., Personnel, Fringe Benefits, Travel).
    - The budget allocations on the line-item budget must relate to the activities proposed in the project narrative, including the work plan.
- To evaluate your adherence to RWHAP Part C Capacity Development statutory budget requirements, submit a program-specific line-item budget for the one-year period of performance (September 1, 2026 – August 31, 2027).
    - Highlight any administrative costs by making them **bold**.

The budget narrative supports the information you provide in Standard Form 424-A. See other required forms. It includes an itemized breakdown and a clear justification of the requested costs. The merit review committee reviews both.

As you develop your budget, also consider the **restrictions on spending funds**. See Funding policies & limitations.

To create your budget narrative, see detailed instructions in Section 3.1.5 of the Application Guide [PDF].

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Attachments

Place your attachments in this order in the Attachments Form. See application checklist to determine if they count toward the page limit.

Unless the instructions below require it, do not submit organizational brochures or other promotional materials (for example, slides, films, clips).

Attachment 1: Proof of non-profit status

If your organization is non-profit, you need to attach proof. We will accept any of the following:

- A copy of a current tax exemption certificate from the IRS.
- A letter from your state's tax department, attorney general, or another state official saying that your group is non-profit and that none of your net earnings go to private shareholders or others.
- A certified copy of your certificate of incorporation. This document must show that your group is non-profit.
- Any of the listed documents for a parent organization. Also include a statement signed by an official of the parent group that your organization is a non-profit affiliate.

Attachment 2: Funding preference documentation

Provide information, including supporting documentation, data, and other details according to the instructions for funding preferences for either rural areas or underserved populations. **HRSA will review the information to determine whether you qualify for a funding preference.** See funding preferences for more information.

Attachment 3: Federally negotiated indirect cost rate (if applicable)

Provide any documents that describe working relationships between your organization and others you mention in your project narrative. If you include documents that confirm actual or pending contracts or agreements, the documents should clearly describe the roles of subrecipients and contractors and any deliverables. It is not necessary to include the entire contents of lengthy agreements, so long as the portions you include describe the working relationship between you and the other organization. Make sure letters of agreement are signed and dated.

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Attachment 4: Biographical sketches

Include biographical sketches for the principal investigator/principal director, project coordinator (if different) and any staff directly responsible for implementing the proposed projects that you describe in Attachment 7.

For key personnel, the biographical sketch should be no more than 1-page. Do not include personally identifiable information.

Attachment 5: Program specific line-item budget

Submit as a PDF document a program-specific line-item budget for the 1-year period of performance. SF-424A Section B is not counted toward the page limit; however, the line-item budget itself does count toward the page limit. Reference section See Section 3.4.1. of the Application Guide [PDF].

Attachment 6: Work plan

Attach the project's work plan for the 12-month period of performance of September 1, 2026 to August 31, 2027. Make sure it includes everything required in the project narrative section.

Attachment 7: Staffing plan and job descriptions

See Section 3.1.7 of the Application Guide [PDF].

Include a staffing plan that provides key information about the staff positions. Include: name, position title, brief background, and the role and responsibilities of the person in your proposed project. For each staff, include the sources of funding for your proposed project and corresponding time and effort. It is recommended to supply this information in the form of a table.

Attachment 8: Agreements with other entities

Provide any documents that describe working relationships between your organization and others you refer to in the proposal. Documents that confirm actual or pending contracts or agreements should clearly describe the roles of the contractors and any deliverable. Make sure you sign and date any letters of agreement.

Attachment 9-15: Other relevant documents

You may use attachments 9 through 15 for any other relevant documentation.

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Other required forms

You will need to complete some other forms. Upload the following forms at Grants.gov. You can find them in the NOFO application package or review them and any available instructions at Grants.gov Forms.

Forms	Submission requirement
Application for Federal Assistance (SF-424)	With application.
Project Abstract Summary form	With application.
Grants.gov Lobbying form	With application.

Form instructions

The application guide has detailed instructions for:

- The Application for Federal Assistance (SF-424).
- The Budget Information for Non-Construction Programs (SF-424A).

Project abstract summary form instructions

Complete the information in the Project Abstract Summary form. Include a short description of your proposed project. Include the needs you plan to address, the proposed services, and the population groups you plan to serve. Indicate the funding amount requested and the name the specific activity.

For more information, see Section 3.1.2 of the Application Guide [PDF].

Important: Public information

When filling out your SF-424 form, pay attention to Box 15: Descriptive Title of Applicant's Project.

We share what you put there with USAspending. This is where the public goes to learn how the federal government spends their money.

Instead of just a title, insert a short description of your project and what it will do.

See instructions and examples.

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Step 4: Understand Review, Selection, and Award

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Application review

Initial review

We will review your application to make sure that it meets eligibility criteria, and the requirements in this NOFO. If your application does not meet eligibility criteria, it will not be funded. If your application does not meet other criteria, we will not fund it.

Merit review

A panel reviews all applications that pass the initial review. You can find more about the merit review process in the Application Guide [PDF]. The members use these criteria.

Criterion	Total number of points = 100
1. Need	10 points
2. Response	35 points
3. Performance reporting and evaluation	15 points
4. Impact	10 points
5. Resources and capabilities	20 points
6. Support requested	10 points

Criterion 1: Need (10 points)

See the project narrative Introduction and Need sections.

The panel will review your application for how well it:

Introduction (3 points)

- States the proposed activity.
- Describes the overall purpose of the proposed project and the need for capacity development funding.
- Explain how the proposed activity will improve access to high-quality primary care for low-income people with HIV.
- Demonstrates that the proposed activity is a brand-new activity that introduces innovative approaches, services, or strategies to the program.

Need (7 points)

- Justifies the need for capacity development funding to address the gaps in organizational capacity or the limitations of current infrastructure.
- Describes the relevant barriers to successfully carry out the project, and the steps to be taken to minimize or overcome the stated barriers.
- Outlines equipment or data system needs.
- Includes proposed changes to the current service delivery system.
- Describes how the lessons learned will be applied.

Criterion 2: Response (35 points)

See the project narrative Approach, and Work plan sections.

The panel will review your application for:

Approach (15 points)

- Clarity of the approach, including specific action steps and the roles of responsible staff or partners, to ensure effective implementation of the proposed activity.
- The extent to which the activities described in the application can address the need and attain the project objectives.
- The description of intent to share or disseminate relevant information and products developed through the funded activity and lessons learned with other providers in the community and collaborators to this project.

Work plan (20 points)

- Clarity of the goal, objectives, and action steps for the 12-month work plan (Attachment 6).
- The structure and completeness, including when each step will be completed and who is responsible for implementation.
- The extent to which the activities described in the application can address the problem and attain the project objectives.

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Criterion 3: Performance reporting and evaluation (15 points)

See the project narrative Performance reporting and evaluation section.

The panel will review your application for:

- Clearness of the evaluation plan to monitor progress towards project goals and objectives, and efficiency of plan to address barriers to implementation.

Criterion 4: Impact (10 points)

See the project narrative Resolving challenges and Sustainability sections.

The panel will review your application for:

Resolving challenges (5 points)

- The clarity of the outline of challenges likely to be encountered in designing and carrying out the activities in the work plan.
- Describes the specific activities or strategies used to mitigate or resolve anticipated challenges in implementing the proposed activity.

Sustainability (5 points)

- The extent to which activities outlined in the work plan can reasonably be completed in the 12-month period of performance.
- The strength of the applicants proposed plan for sustaining activities, without additional federal funds, beyond the federal funding period

Criterion 5: Resources and capabilities (20 points)

See the project narrative Organizational information and Performance reporting and evaluation sections.

The panel will review your application to determine the extent to which:

Organizational information (10 points)

- The organization demonstrates the ability to secure agreements with community-based organizations, health care providers, and consultant services needed to successfully achieve the proposed project.
- The organization demonstrates the ability to purchase equipment and execute contracts for services for this project within a reasonable timeframe to complete project activities.

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Staffing plan (10 points)

- The staffing plan (Attachment 7) is consistent with the proposed activity.
- Staffing plan is adequate or sufficient for meeting the proposed project goals and objectives.

Criterion 6: Support requested (10 points)

See the Budget and budget narrative section.

The panel will review your application to determine:

- How reasonable the proposed budget is for the period of performance.
- How reasonable costs are and how well they align with the project's scope.
- How sufficient the time is for key staff to spend on the project to achieve project objectives.

We do not consider **voluntary** cost sharing during merit review.

Risk review

Before making an award, we review your award history to assess risk. We need to ensure all prior awards were managed well and demonstrated sound business practices. We:

- Review any applicable past performance.
- Review audit reports and findings.
- Analyze the budget.
- Assess your management systems.
- Ensure you continue to be eligible.
- Make sure you comply with any public policies.

We may ask you to submit additional information.

As part of this review, we use SAM.gov Entity Information Responsibility/Qualification to check your history for all awards likely to be more than $250,000 over the period of performance. You can comment on your organization's information in SAM.gov. We'll consider your comments before making a decision about your level of risk.

If we find a significant risk, we may choose not to fund your application or to place specific conditions on the award.

For more details, see 2 CFR 200.206.

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Funding priorities

A funding priority adds points to merit review scores if we determine that the application meets the listed criteria. Qualifying for a funding priority does not guarantee that your application will be successful.

Priority 1: Not currently funded by this opportunity (2 Points)

We will give you a funding priority if:

Your organization does not hold an active award under this opportunity at the time you apply.

Priority 2: Never funded by this opportunity (2 Points)

We will give you a funding priority if:

Your organization has never received an award under this opportunity.

Priority 3: Alignment with Ending the HIV Epidemic in the U.S. (EHE) initiative (2 points)

We will give you funding priority if the following is met:

Your proposal is in an EHE priority state.

Selection process

When making funding decisions, we consider:

- The amount of available funds.
- Assessed risk.
- Merit review results. These are key in making decisions but are not the only factor.
- The larger portfolio of HRSA-funded projects, including project type and geographic distribution.
- The funding priorities, funding preferences, and special considerations listed.
- Alignment with HRSA Mission and Strategic Priorities

We may:

- Fund out of rank order.
- Fund applications in whole or in part.
- Fund applications at a lower amount than requested.
- Decide not to allow a recipient to subaward if they may not be able to monitor and manage subrecipients properly.
- Choose to fund no applications under this NOFO.

Additionally, we may not make an award if you are delinquent on two or more Single Audit Reports.

You cannot appeal a denial, or the amount of funds awarded.

Funding preferences

This program includes funding preferences, based on section 2654(c)(3) of the PHS Act. If we determine that your application meets these criteria, we will move it up in our ranking of fundable applications. Qualifying for a funding preference does not guarantee that you will receive funding.

HRSA will grant only **one** funding preference to any qualified applicant that justifies its qualification.

Qualifications to meet the funding preferences:

- **Attachment 2 is required for all applicants.**
  - HRSA will review the information and determine whether your application qualifies for a funding preference.
  - Receipt of a funding preference is not a guarantee of funding.

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Qualification 1: Rural areas

The criterion for this funding preference is based on the provision of HIV primary care services in a rural area including:

- RWHAP recipients are defined as rural if their service area (in part or in whole) or main organizational address is in a HRSA Federal Office of Rural Health Policy (FORHP)-designated rural area.
- FORHP classifies all non-metropolitan counties, as defined by the Office of Management and Budget, as rural.
- FORHP uses Rural-Urban Commuting Area (RUCA) codes to identify other rural areas.
- For more information about **what defines a rural area**, visit FORHP's website.
- To determine if your organization **serves a rural area**, refer to FORHP's Rural Health Analyzer.
    - If your service area (either in part or in whole) or main organizational address **is defined as rural**, print out a screenshot of the result and include the printout as supporting documentation in .pdf format in Attachment 2.
    - If your organization **does not provide HIV primary care services in a rural area**, you can indicate "Not applicable" in Attachment 2.

Qualification 2: Underserved populations

The criterion for this funding preference is the provision of HIV primary care services to underserved populations including:

- Underserved populations include communities and subpopulations that do not have access to adequate HIV primary care services, as defined by HAB PCN 16-02.
- These gaps in the provision of HIV primary care services must be defined and documented in Attachment 2.
- State in Attachment 2 whether your organization provides HIV primary care services for underserved populations.
- You must provide all information to be considered for this funding preference:
    - Data and information on overall HIV primary care gaps, including any inadequate or unavailable HIV primary care services, as defined by HAB PCN 16-02.
    - Data and information on specific HIV subpopulations served by your organization that are disproportionately affected by inadequate or unavailable HIV primary care services, as defined by HAB PCN 16-02.
- If your organization does not provide HIV primary care services to underserved populations, you can indicate "Not applicable" on Attachment 2.

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Award notices

We issue Notices of Award (NOA) on or around the start date listed in the NOFO. See "how we make awards" in the Application Guide [PDF] for more information.

By drawing down funds, you accept the terms and conditions of the award.

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Step 5: Submit Your Application

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Application submission and deadlines

Your organization's authorized official must certify your application. See the section on finding the application package to make sure you have everything you need.

Application deadline

You must submit your application by 06/01/2026, at 11:59 p.m. ET.

Grants.gov creates a date and time record when it receives applications.

If you need a deadline extension, see "requesting a waiver" in the Application Guide [PDF].

Submission method

Grants.gov

You must submit your application through Grants.gov. You may do so using Grants.gov Workspace. This is the preferred method. For alternative online methods, see Applicant System-to-System.

For instructions on how to submit in Grants.gov, see the Quick Start Guide for Applicants. Make sure that your application passes the Grants.gov validation checks, or we may not get it. Do not encrypt, zip, or password protect any files.

If Grants.gov rejects your application due to errors, you must correct and resubmit before the deadline.

If you want to know more about correcting errors or tracking your application, you can refer to the Application Guide [PDF].

Have questions? Go to Contacts and Support.

Other submissions

Intergovernmental review

This NOFO is not subject to Executive Order 12372, Intergovernmental Review of Federal Programs. No action is needed.

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Step 6: Learn What Happens After Award

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Post-award requirements and administration

Administrative and national policy requirements

There are important rules you need to know if you get an award. You must follow:

- All terms and conditions in the Notice of Award (NOA). We incorporate this NOFO by reference.
- The regulations at 2 CFR Part 200, Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards, modifications at 2 CFR Part 300, and any superseding regulations.
- The HHS Grants Policy Statement. Your NOA will reference this document. If there are any exceptions to the GPS, they'll be listed in your NOA.
- All federal statutes and regulations relevant to federal financial assistance, including those highlighted in HHS Grants Policy Statement, Appendix D: HHS Administrative and National Policy Requirements.
- The requirements for performance management in 2 CFR 200.301.
- All anti-discrimination laws: By applying for or accepting federal funds from HHS, you certify compliance with all federal antidiscrimination laws and these requirements. Complying with those laws is a material condition of receiving federal funding streams. You are responsible for ensuring subrecipients, contractors, and partners also comply.
- Any applicable statutory provisions.
- The Assurances (standard certification and representations) included in the annual SAM registration.

Required alignment with HRSA mission and strategic priorities

Recipients must use funds awarded under this NOFO to implement program goals or agency priorities in accordance with the HRSA vision, mission, core values, and strategic priorities, where authorized by law.

Funded activities must advance HRSA's vision of protecting and improving the health and well-being of Americans. The particular focus is on those who are medically vulnerable or live in areas with limited access to care. HRSA's duty is to serve

wisely, effectively, and with measurable results that justify every taxpayer dollar invested.

Consistent with HRSA's priorities, in carrying out any project funded under this NOFO, the recipient must adhere to the following principles, where they are consistent with the authority and scope of the award and its activities:

- **Gold standard science:** Design and deliver services using gold standard evidence-based and evidence-informed approaches, establish measurable performance goals, and use data to monitor outcomes and drive continuous improvement.
- **Program integrity and fiscal stewardship:** Recipients must:
  - Administer funds in accordance with all applicable federal statutes, regulations, and award conditions.
  - Maintain strong internal controls.
  - Prevent waste, fraud, and abuse.
- **Partnership and local leadership:** Coordinate with state, tribal, territorial, local, and community partners, as appropriate, and tailor services to meet community-identified needs while respecting local decision-making authority.

Recipients must manage any project awarded under this NOFO in accordance with the following objectives in programs authorized to advance them:

Make America Healthy Again (MAHA): HRSA prioritizes the health and well-being of all Americans by supporting common-sense, evidence-based health policies that promote:

- Personal responsibility.
- Strong families and communities.
- Proper nutrition.
- The prevention and management of chronic disease, while ensuring access to high-quality, affordable physical and mental health care.

Child protections, biological integrity, parental rights, and lawful use of funds: HRSA prioritizes safeguarding children's health and safety by:

- Not supporting medical interventions for gender dysphoria in minors that lack a strong evidence base.
- Applying sex-based definitions grounded in biological reality.
- Supporting parental authority, transparency, and choice in education, including school-based health centers that respect parental rights and religious upbringing.
- Ensuring taxpayer funds are not used to promote or support elective abortions, consistent with federal law and the Hyde Amendment.

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Advancing evidence-based, merit-driven, and ethically grounded health care: HRSA will prioritize unbiased, transparent science; merit-based workforce opportunities; and programs that demonstrate measurable outcomes, while deprioritizing organizations with:

- Conflicts of interest.
- "Harm reduction models."
- Housing-first approaches.
- Activities that facilitate illegal drug use or unsafe medical practices.

Promoting public safety, lawful use of federal funds, and national health priorities: To the extent permitted by law, HRSA will align funding with administration priorities by:

- Supporting ending the HIV epidemic through authorized, evidence-based care.
- Reserving benefits for eligible individuals.
- Discouraging illegal immigration and unsafe community practices.
- Prioritizing recipients that enforce public safety, address serious mental illness and substance use through treatment and recovery, and reduce homelessness responsibly.

To the extent allowable by law, under awards, HRSA will give priority to states and municipalities for programs to:

- Enforce prohibitions on open illicit drug use.
- Enforce prohibitions on urban camping and loitering.
- Enforce prohibitions on urban squatting.
- Enforce, and where necessary, adopt, standards that address individuals who are a danger to themselves or others and suffer from serious mental illness or substance use disorder, or who are living on the streets and cannot care for themselves. The approach must be through assisted outpatient treatment or by moving them into treatment centers or other appropriate facilities through civil commitment or other available means, to the maximum extent permitted by law.

HRSA will implement these priorities consistent with applicable laws, regulations, court orders, and any required procedures.

The recipient must demonstrate ongoing compliance with these priorities, in all programs that are authorized to advance them, through program design, implementation, reporting, and evaluation.

Failure to meaningfully align funded activities with the applicable requirements may result in corrective action, additional reporting requirements, or other actions consistent with federal grant regulations at 2 CFR. part 200 and the terms and

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conditions of this award. This includes termination under CFR. 200.340(a)(4) if an award no longer effectuates the program goals or agency priorities.

Cybersecurity

If awarded, you must develop plans and procedures, modeled after the NIST Cybersecurity framework, to protect HHS systems and data. See details here.

HIT

Successful applicants under this NOFO agree that:

Where award funding involves:	Recipients and subrecipients are required to:
Implementing, acquiring, or upgrading health IT for activities funded by any entity	Use health IT that meets standards and implementation specifications adopted in 45 CFR 170, Subpart B, if such standards and implementation specifications can support the activity. Visit to 45 CFR 170, Subpart B learn more.
Implementing, acquiring, or upgrading health IT for activities by eligible clinicians in ambulatory settings, or hospitals, eligible under Sections 4101, 4102, and 4201 of the HITECH Act	Use health IT certified under the ONC Health IT Certification Program if certified technology can support the activity.

If standards and implementation specifications adopted in 45 CFR part 170, Subpart B cannot support the activity, recipients and subrecipients are encouraged to use health IT that meets non-proprietary standards and implementation specifications developed by consensus-based standards development organizations. This may include standards identified in the ONC Interoperability Standards Advisory.

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Reporting

If you are funded, you will have to follow the reporting requirements in “reporting” section of the Application Guide [PDF]. The NOA will provide specific details.

You must also follow these program-specific reporting requirements:

- Information relevant to program-specific goals and progress on the work plan (for example, number of clients served, partnerships)
- Impact of the overall project
- The degree to which the recipient achieved the mission, goal, and objectives outlined in the program
- Recipient accomplishments
- Barriers encountered
- Responses to summary questions regarding the recipient’s overall experiences during the 1-year period of performance.
- Recipients will be expected to provide end-of-the-period of performance outcome data and demonstrate the impact of the project’s activity.

Further information will be available in the NOA.

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Agency contacts

Program and eligibility

Brian Fitzsimmons
Public Health Advisor
Attn: Ryan White HIV/AIDS Program Part C Capacity Development Program
Health Resources and Services Administration
AskPartCCapacity@hrsa.gov
301-945-9820

Financial and budget

Bria Haley
Grants Management Specialist
Division of Grants Management Operations
Office of Financial Assistance and Acquisition Management (OFAAM)
Health Resources and Services Administration
BHaley@hrsa.gov
301-443-3778

HRSA Contact Center

Open Monday through Friday, 7 a.m. to 8 p.m. ET, except for federal holidays.
Call: 877-464-4772 / 877-Go4-HRSA
TTY: 877-897-9910

Electronic Handbooks Contact Center

Help with systems

Grants.gov

Grants.gov provides 24/7 support. You can call 800-518-4726, search the Grants.gov Knowledge Base, or email Grants.gov for support. Hold on to your ticket number.

SAM.gov

If you need help, you can call 866-606-8220 or live chat with the Federal Service Desk.

Helpful websites

- Application Guide [PDF]
- HRSA Grants page
- HHS Tips for Preparing Grant Proposals
- Frequently Asked Questions
- Applicant Training

EXHIBIT D

Notice of Funding Opportunity

Application due 07/10/2026

HRSA
Health Resources & Services Administration

HIV/AIDS Bureau
Division of Community HIV/AIDS Programs

Ryan White HIV/AIDS Program Part F Dental Reimbursement Program

Opportunity number: HRSA-26-085

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Before you begin

If you believe you are a good candidate for this funding opportunity, secure your SAM.gov and Grants.gov registrations now. If you are already registered, make sure your registrations are active and up-to-date.

SAM.gov registration (this can take several weeks)

You must have an active account with SAM.gov. This includes having a Unique Entity Identifier (UEI).

See Step 2: Get Ready to Apply

Grants.gov registration (this can take several days)

You must have an active Grants.gov registration. Doing so requires a Login.gov registration as well.

See Step 2: Get Ready to Apply

Apply by the application due date

Applications are due by 11:59 p.m. Eastern Time on 07/10/2026.

To help you find what you need, this NOFO uses internal links. In Adobe Reader, you can go back to where you were by pressing Alt + Left Arrow (Windows) or Command + Left Arrow (Mac) on your keyboard.

All activities proposed in your application and budget narrative must align with applicable law, including but not limited to statutes, executive orders, federal regulations and applicable judicial holdings. Accordingly, discretionary awards shall not be used to fund, promote, encourage, subsidize, or facilitate: racial preferences or other forms of racial discrimination by the recipient, including activities where race or intentional proxies for race will be used as a selection criterion for employment or program participation; denial by the recipient of the sex binary in humans, or the belief that sex is a chosen or mutable characteristic; illegal immigration; or any other initiatives that compromise public safety. If an application does not align, the application will not receive funding to the extent permitted by law and applicable court orders.

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Step 1:
Review the Opportunity

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Basic information

Health Resources Services Administration

HIV/AIDS Bureau

Division of Community HIV/AIDS Programs

Dental reimbursement program.

Summary

The Dental Reimbursement Program reimburses certain costs incurred by eligible entities that have provided uncompensated or partially uncompensated oral health care to people with HIV during a specified one-year period. Funds will be distributed among eligible applicants by comparing each eligible applicant's number of patients with HIV served and unreimbursed oral health care costs to the total number of patients served and costs incurred by all eligible applicants.

Funding details

Application Types: New

Expected total available funding in FY 2026: $9,000,000

Expected number and type of awards: 50 grants

Funding range per award: Amount varies.

We plan to fund awards in a single six-month budget period. The period of performance is 9/1/2026 to 2/28/2027.

Have questions?
Go to Contacts and Support.

Key facts

Opportunity name:
Ryan White HIV/AIDS Program Part F Dental Reimbursement Program

Opportunity number:
HRSA-26-085

Announcement version:
Initial

Federal assistance listing:
93.924

Key dates

NOFO issue date:
06/08/2026

Informational webinar:
Join the Webinar

Application deadline:
07/10/2026

Expected award date:
09/01/2026

Expected start date:
09/01/2026

See other submissions for other time frames that may apply to this NOFO.

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Eligibility

You can apply if you are an accredited domestic dental school and other accredited domestic dental education program, such as dental hygiene program, or those sponsored by a school of dentistry, a hospital with a dental education program that is accredited by the Commission on Dental Accreditation, or a public or private institution that offers postdoctoral training in the specialties of dentistry, advanced education in general dentistry, or a dental-general practice residency. Dental education programs must be accredited by the Commission on Dental Accreditation.

Types of eligible organizations

These types of domestic organizations may apply:

- Public and State controlled institutions of higher education.
- Private institutions of higher education.
- Others. (See text field entitled “Additional Information on Eligibility” for clarification.)

Additional information on eligibility

“Domestic” means the 50 states, the District of Columbia, the Commonwealth of Puerto Rico, the Northern Mariana Islands, American Samoa, Guam, the U.S. Virgin Islands, the Federated States of Micronesia, the Republic of the Marshall Islands, and the Republic of Palau.

Individuals are not eligible applicants under this NOFO.

Completeness and responsiveness criteria

We will review your application to make sure it meets these basic requirements to move forward in the competition.

We will not consider an application that:

- Is from an organization that does not meet all eligibility criteria.
- Is submitted after the deadline.
- **Applications that do not meet the following requirements may be deemed ineligible**:
    - Failure to include the total unreimbursed costs of oral health care provided to low-income people with HIV from July 1, 2024, through June 30, 2025, in fields 18a and 18g of the SF-424 application.

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- Failure to submit the required Dental Services Report information on or before the application deadline on the Dental Services Report website.
- Discrepancies between the unreimbursed costs reported on the Dental Services Report and the SF-24 application. HRSA will verify these amounts, and if they do not match, the application may be deemed ineligible.

Application limits

You may not submit more than one application. If you submit more than one application, we will only accept the last on-time submission.

Cost sharing

This program has no cost-sharing requirement. If you choose to share in the costs of the project, we will not consider it during merit review. Recipients agree that once committed, cost sharing amounts are enforceable and subject to reporting and auditing requirements under 2 CFR 200.

Maintenance of effort

Federal funds must add to any existing non-federal funds for your proposed activities. If you receive an award, you will have to spend at least as much as you spent in the last fiscal year before the award. Section 2692(b)(4) of the PHS Act requires this. We will enforce these statutory requirements through all available mechanisms. You must provide supporting documentation of your maintenance of effort in your attachments.

RWHAP Part F DRP funds are not intended to be the sole source of support for oral health care services for people with HIV. The RWHAP statute requires DRP recipients to maintain expenditures of state funds (if any) for DRP-related activities at a level equal to or greater than the fiscal year preceding the DRP reimbursement period. The maintenance of effort (MOE) requirement is important in ensuring that RWHAP funds are used to supplement, not supplant, state funds allotted for oral health care services for people with HIV.

Post-award requirements

Before you apply, make sure you understand the requirements that come with an award.

See Step 6: Learn What Happens After Award for information on regulations that apply, reporting, and more.

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Program description

Purpose

Our purposes are to:

1. Improve access to oral health care services for low-income people with HIV.
2. Support related education and training for the delivery of dental care to people with HIV.

This program will reimburse certain costs incurred by eligible entities that have provided uncompensated or partially uncompensated oral health care to people with HIV from July 1, 2024, through June 30, 2025.

Funding opportunity goals

- Reduce the new HIV infections in the U.S. by focusing on HIV care and treatment strategies so that people with HIV reach viral suppression and therefore do not sexually transmit HIV.
- Help low-income people with HIV by providing: medical care, medications , and support service to help them stay in care .
- Reach people with HIV who are out of care by leveraging partnerships, focusing interventions, and engaging communities.

Background

The Ryan White HIV/AIDS Program

The Ryan White HIV/AIDS Program (RWHAP) has five statutorily defined Parts that provide grants to states, cities, counties, local clinics, and community-based organizations. The grants fund medical care, medication, and essential support services, to meet the needs of people with HIV and family members affected by HIV. Together these grants provide a comprehensive system of care to ensure low-income people with HIV have access to services for early diagnosis of HIV, linkage to care, medically appropriate treatment, retention in care, and sustained viral suppression (a very low or undetectable amount of HIV in the blood).

For nearly four decades, the RWHAP has funded services to provide HIV primary health care, medication, and essential support services, including mental health care, transportation, case management, nutrition, and housing. These services support clients to enter and remain in care, access medications, and reach viral suppression, reducing transmission and lowering health care costs.

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Ending the HIV Epidemic

Launched in 2020, the Ending the HIV Epidemic in the U.S. (EHE) initiative further expands federal efforts to reduce HIV transmission. For the RWHAP, the EHE initiative expands the program's ability to meet the needs of clients, specifically focusing on linking people with HIV who are either newly diagnosed, diagnosed but currently not in care, or are diagnosed and in care but not yet virally suppressed, to the essential HIV care, treatment, and support services needed to help them reach viral suppression.

Making America Healthy Again

The Ryan White HIV/AIDS Program helps advance the Making America Healthy Again (MAHA) priorities by:

- **Expanding access to primary care** for people with HIV, particularly those with low incomes, and by strengthening the health workforce.
- **Fighting the chronic disease epidemic** by providing HIV medical care, treatment, and support services to people with HIV.
- **Supporting improved nutrition** by providing patient-centered focused medical nutrition therapy and food services.
- **Supporting disease prevention** through HIV care and treatment services that help people reach viral suppression so they live longer, healthier lives and do not transmit HIV.

Key accomplishments

- **Nearly 602,000 people with HIV** in the U.S. received life-saving care, medication, and essential support services through the RWHAP, representing over half of all diagnosed with HIV in the U.S. This is an increase of nearly 26,000 clients.
- **More than 91%** of Ryan White HIV/AIDS Program patients receiving HIV medical care were virally suppressed in 2024. This is up from 69.5% of patients virally suppressed in 2010 and significantly higher than the 67.2% virally suppressed nationally among all people with diagnosed HIV.
- **More than 47%** of Ryan White HIV/AIDS Program clients are aged 50 years and older, demonstrating the program's success in supporting older clients and its commitment to addressing the unique needs of people aging with HIV.

Program requirements and expectations

- **Dental Services Report** — You must submit a Dental Services Report electronically. For detailed instructions, see Appendix.
- **Patient payment for services** — Recipients must have consistent policies and procedures related to verification of patients' financial status.
- **Payor of last resort and eligibility determination** — With the exception of programs administered by or providing the services of the Indian Health Service, the RWHAP is the payor of last resort. Recipients may not use RWHAP Part F DRP funds for a service if payment has been made, or reasonably can be expected to be made, by a state compensation program, under an insurance policy, under a Federal or State health benefits program, or by an entity that provides health services on a pre-paid basis.
    - Eligibility and confirmation should be determined in accordance with guidelines in HAB PCN 21-02 Determining Client Eligibility & Payor of Last Resort [PDF] in the RWHAP. HRSA HAB expects all RWHAP recipients and subrecipients to establish, implement, and monitor policies and procedures to determine client eligibility.
    - To extend finite RWHAP grant resources to low-income people with HIV, recipients and subrecipients must vigorously pursue and rigorously document enrollment into, and subsequent reimbursement from, health care coverage for which their clients may be eligible. Examples include Medicaid, Medicare, Children's Health Insurance Program (CHIP), state-funded HIV programs, employer-sponsored health insurance coverage, and health plans offered through other private health insurers.
- **Recipients cannot use RWHAP Part F DRP funds to supplement the maximum cost allowance for services reimbursed by third party payments such as Medicaid, Medicare, or other insurance programs.** Please note that recipients cannot use direct or indirect federal funds such as RWHAP Parts A, B, C, D and Part F Community Based Dental Partnership Program (CBDPP) to duplicate reimbursement for services funded under Part F DRP. Additionally, recipients cannot bill RWHAP Parts A, B, C, D or Part F CBDPP for services reimbursed by RWHAP Part F DRP.
- **Other financial management issues** — Funds received from DRP must be allocated to the accredited dental schools and other accredited dental education programs (see Eligibility section that provide oral health services to low-income people with HIV. HRSA expects that these reimbursement funds will provide expanded access to oral health care for people with HIV.

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- **Education and training** — RWHAP Part F DRP awarded applicants must ensure HIV-related oral health education and training for dental students, dental hygiene students, dental residents, or other dental providers. Education and training curricula should focus on the provision of comprehensive oral health care for people with HIV.

Statutory authority

42 U.S.C. § 300ff-111(b) (Title XXVI, § 2692(b) of the Public Health Service (PHS) Act).

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Award information

Funding policies and limitations

Changes in HHS regulations

As of October 1, 2025, HHS has adopted 2 CFR Part 200, with some modifications included in 2 CFR Part 300. These regulations replace those in 45 CFR Part 75.

Policies

- To make an award, funding must be available and allocated for this program and purpose, at which point we will move forward with the review and award process.
- Have clear policies and good financial practices to avoid spending HRSA funds on unallowable activities. Like other award rules, we may audit your policies, procedures, and controls.

General limitations

- For guidance on some types of costs we do not allow or restrict, see
  - Project Budget Information in Section 3.1. of the Two-Tier Application Guide [PDF].
  - 2 CFR Part 200 Subpart E - General Provisions for Selected Items of Cost.
  - Allowable and Unallowable Costs and Activities, in the HHS Grants Policy Statement.
- All costs must be reasonable, necessary, allocable to the award, and adequately documented (2 CFR 200.403).
- You cannot earn profit from the federal award. See 2 CFR § 200.400(g).
- Current appropriations law includes a salary limit of $228,000 as of January 2026 that applies to this program. You may pay salaries at a higher rate if the rate beyond the salary rate limit (Executive Level II) is paid with non-HHS funds. For help calculating salaries under this limit, read more at “salary rate limitation” in the Two-Tier Application Guide [PDF].

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Program-specific statutory or regulatory limitations

You cannot use funds under this notice for the following:

- Funding restrictions included in PCN 16-02.
- Services that must be paid for by other sources, consistent with the RWHAP payor of last resort requirement in PCN 21-02.
- Payments for inpatient hospitals, nursing homes, and other long-term care facilities.
- Cash payments to intended clients of RWHAP services.
- Purchase of, or improvement to land.
- Purchase, construction, or major alterations or renovations on any building or other facility (see 2 CFR 200 – subpart A Definitions).
- PrEP or non-occupational Post-Exposure Prophylaxis (nPEP) medications or the related medical services. As outlined in the updated November 16, 2021 RWHAP and PrEP program letter.
- Purchase of sterile needles and syringes for the purpose of hypodermic injection of any illegal drug use. Some aspects of syringe services programs are allowable with HRSA's prior approval and in compliance with HHS and HRSA policy. See Syringe Services Programs.
- Development of materials designed to directly promote or encourage intravenous drug use or sexual activity, whether homosexual or heterosexual.
- Research.
- Foreign travel.

You must have policies, procedures, and financial controls in place. Anyone who receives federal funding must comply with legal requirements and restrictions, including those that limit specific uses of funding.

- Follow the list of statutory restrictions on the use of funds in Section 4.1 (Funding Restrictions) of the Application Guide.
    - We may audit the effectiveness of these policies, procedures, and controls. 2 CFR § 200.216 prohibits certain telecommunications and video surveillance services or equipment.
    - For details, see the HRSA Grants Policy Bulletin Number: 2021-01E.

See Manage Your Grant for other information on costs and financial management.

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Indirect costs

Indirect costs are costs you charge across more than one project that cannot be easily separated by project. For example, this could include utilities for a building that supports multiple projects.

To incur indirect costs, you can select one of two methods:

Method 1 – Approved rate. You currently have an indirect cost rate approved by your cognizant federal agency at the time of award.

Method 2 – *De minimis* rate. Per 2 CFR § 200.414(f), if you do not have a current negotiated indirect cost rate, you may elect to charge a ***de minimis*** rate. If you choose this method, costs included in the indirect cost pool must not be charged as direct costs.

This rate is up to 15% of modified total direct costs (MTDC). See 2 CFR § 200.1 for the definition of MTDC. You can use this rate indefinitely for all your federal awards or until you choose to receive a negotiated rate.

Consider your indirect costs when developing your budget.

Program income

Program income is money earned as a result of your award-supported project activities. You must use any program income you generate from awarded funds for approved project-related activities. Find more about program income at 2 CFR 200.307.

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Step 2:
Get Ready to Apply

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Get registered

SAM.gov

You must have an active account with SAM.gov to apply. SAM.gov registration can take several weeks. Begin that process today.

To register:

- Go to SAM.gov Entity Registration and select Get Started. From the same page, you can also select the Entity Registration Checklist for the information you will need to register.
- You must agree to the financial assistance general certifications and representations specifically. Those for contracts are different.

When you register, you will also receive your required Unique Entity Identifier (UEI).

Once you register:

- You will have to maintain your registration throughout the life of any award.
- If your organization has multiple UEIs, use the one associated with your physical location.

If you need additional information about user roles in SAM.gov, see “Get registered: SAM.gov user roles” in the Application Guide [PDF].

Grants.gov

You must also have an active account with Grants.gov. You can see step-by-step instructions at the Grants.gov Quick Start Guide for Applicants and How to Apply for Grants.

Find the application package

The application package has all the forms you need to apply. You can find it online. Go to Grants Search at Grants.gov and search for opportunity number HRSA-26-085.

After you select the opportunity, we recommend that you click the Subscribe button to get updates.

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Application writing help

Visit HHS Tips for Preparing Grant Proposals.

Visit HRSA's How to Prepare Your Application page for more guidance.

See Apply for a Grant for other help and resources.

FAQs will be posted on our TA webpage after the webinar.

Join the webinar

Webinar Information will be posted to the Related Documents tab on Grants.gov. We recommend you "Subscribe" to the NOFO on Grants.gov to receive updates when documents are posted.

Have questions? Go to Contacts and Support.

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Step 3: Build Your Application

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Application checklist

There are two types of forms in Grants.gov.

- Some forms allow you to upload components of your application to the form. These include components like your project narrative, budget and budget narrative, and attachments, as applicable.
- Other forms are more typical, fill-in-the-blank forms.

Make sure that you have everything you need to apply.

Narratives

Component	Grants.gov form	Included in page limit*?
☐ Attachments	Insert each in the Other Attachments form	Yes, unless marked otherwise
☐ Other required forms	Upload using each required form	No
☐ Dental Services Report	Submit this on the Dental Services Report website	No

Attachments

Insert each in the Attachments form in this order.

Component	Included in page limit*?
☐ 1. Maintenance of effort	Yes
☐ 2. Other relevant documents (if applicable)	Yes

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Other required forms

Upload using each required form in Grants.gov.

Forms	Submission requirement
☐ Application for federal assistance (SF-424)	With application.
☐ Project/Performance site location(s)	With application.
☐ Project abstract summary form	With application.
☐ Grants.gov lobbying form	With application.
☐ Key contacts	With application.

*Only what you attach in these forms counts toward the page limit. The forms themselves do not count.

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Application contents and format

This section includes guidance on each component found in the application checklist.

Application page limit: 10

Submit your information in English and express whole number budget figures using U.S. dollars.

Required format

Required format for project summary, project narrative, budget narrative, and attachments.

Font: A readable font like Arial, Courier, CG Times, or Times New Roman.

File format: We only accept the following document formats:

- .PDF - Adobe Portable Document Format
- .DOC/.DOCX - Microsoft Word
- .RTF - Rich Text Format
- .TXT - Text
- .WPD - Word Perfect Document
- .XLS/.XLSX - Microsoft Excel
- .VSD - Microsoft Visio

Size: 12-point font
Footnotes, charts, graphics, and budget tables may be 10-point or higher.

Ink color: Black

Spacing: Single-spaced, including all text and tables.

Alignment: Left

Headings: Bold all headings and align left.

Size: 8.5 x 11 (Make sure the print area is set and allows printing to 8.5 x 11.)

Margins: 1-inch on all sides

Footer: On each page as the footer, include your organization's name and page numbers. If a competing continuation or competing supplement, also include your 10-digit award number.

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Page numbering:

- Do not number the standard OMB-approved forms.
- Number each attachment page sequentially (that is, 1, 2, 3).
- Reset the numbering for each attachment.
- Treat each attachment as a separate section.

File names: You can find guidance for naming your files in the Application Guide.

See the reporting section for more information.

Attachments

Place your attachments in this order in the Attachments Form. See application checklist to determine if they count toward the page limit.

Unless the instructions below require it, do not submit organizational brochures or other promotional materials (for example, slides, films, clips).

Attachment 1: Maintenance of effort documentation

Counts toward page limit.

You must maintain state funds (if any) that support proposed activities. These include cash, in-kind, and other contributions. If there were no state funds expended, enter zero. Do not include any federal funds. See maintenance of effort requirement.

You must provide a baseline aggregate expenditure of state funds for the most recently completed fiscal year prior to the application deadline and estimates for the following fiscal year using a chart like the one shown in this section.

As an example, if your fiscal year begins July 1, you report actual expenditures of state funds for oral health care services for people with HIV from July 1, 2024, through June 30, 2025, in column one. In column two, you report estimated expenditures for the next fiscal year (July 1, 2025, through June 30, 2026).

Additionally, provide a brief description of the methodology your institution or program used to calculate MOE for oral health care services for low-income people with HIV. Provide a description of consistent data set(s) of state expenditures for oral health care services for low-income people with HIV and a brief narrative of any changes from the previous FY and the projected FY spending.

Use this sample format to provide the maintenance of effort documentation.

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FY before application: Actual nonfederal expenditures	First FY of award: Estimated nonfederal expenditures
$	$

Attachment 2: Other relevant documents (if applicable)

Include here any other documents that are relevant to your application.

Other required forms

You will need to complete some other forms. Upload the following forms at Grants.gov. You can find them in the NOFO application package or review them and any available instructions at Grants.gov Forms.

Forms	Submission requirement
Application for federal assistance (SF-424)	With application.
Project/performance site location(s)	With application.
Project abstract summary form	With application.
Grants.gov lobbying form	With application.
Key contacts	With application.

Form instructions

The application guide has detailed instructions for:

- The Application for Federal Assistance (SF-424).

Project abstract summary form instructions

Complete the information in the Project Abstract Summary form. For more information, see Section 3.1.2 of the Application Guide [PDF] .

Please name your project title “FY 2026 RWHAP Part F Dental Reimbursement Program” and include the following information:

- The total unreimbursed costs of oral health care provided to people with HIV from July 1, 2024, through June 30, 2025, that are entered in fields 18a and 18g of the SF-424 Application for Federal Assistance. This amount should also match the unreimbursed cost reported on Tab Two of the DSR.

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Important: Public information

When filling out your SF-424 form, pay attention to Box 15: Descriptive Title of Applicant's Project.

We share what you put there with USAspending. This is where the public goes to learn how the federal government spends their money.

Instead of just a title, insert a short description of your project and what it will do.

See instructions and examples.

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Step 4: Understand Review, Selection, and Award

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Application review

Initial review

We will review your application to make sure that it meets eligibility criteria, and the requirements in this NOFO. If your application does not meet eligibility criteria, it will not be funded. If your application does not meet other criteria, we will not fund it.

Risk review

Before making an award, we review your award history to assess risk. We need to ensure all prior awards were managed well and demonstrated sound business practices. We:

- Review any applicable past performance.
- Review audit reports and findings.
- Analyze the budget.
- Assess your management systems.
- Ensure you continue to be eligible.
- Make sure you comply with any public policies.

We may ask you to submit additional information.

As part of this review, we use SAM.gov Entity Information Responsibility/Qualification to check your history for all awards likely to be more than $250,000 over the period of performance. You can comment on your organization's information in SAM.gov. We'll consider your comments before making a decision about your level of risk.

If we find a significant risk, we may choose not to fund your application or to place specific conditions on the award.

For more details, see 2 CFR 200.206.

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Selection process

When making funding decisions, we consider:

- The amount of available funds.
- Assessed risk.
- Alignment with HRSA Mission and Strategic Priorities

We may:

- Fund applications in whole or in part.
- Fund applications at a lower amount than requested.
- Choose to fund no applications under this NOFO.

- Additionally, we may not make an award if you are delinquent on two or more Single Audit Reports.

You cannot appeal a denial, or the amount of funds awarded.

Award notices

We issue Notices of Award (NOA) on or around the start date listed in the NOFO. See "how we make awards" in the Application Guide [PDF] for more information.

By drawing down funds, you accept the terms and conditions of the award.

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Step 5: Submit Your Application

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Application submission and deadlines

Your organization's authorized official must certify your application. See the section on finding the application package to make sure you have everything you need.

Application deadline

You must submit your application by 07/10/2026, at 11:59 p.m. ET.

Grants.gov creates a date and time record when it receives applications.

If you need a deadline extension, see "requesting a waiver" in the Application Guide [PDF] .

Submission method

Grants.gov

You must submit your application through Grants.gov. You may do so using Grants.gov Workspace. This is the preferred method. For alternative online methods, see Applicant System-to-System.

For instructions on how to submit in Grants.gov, see the Quick Start Guide for Applicants. Make sure that your application passes the Grants.gov validation checks, or we may not get it. Do not encrypt, zip, or password protect any files.

If Grants.gov rejects your application due to errors, you must correct and resubmit before the deadline.

If you want to know more about correcting errors or tracking your application, you can refer to the Application Guide [PDF] .

Have questions? Go to Contacts and Support.

Other submissions

Intergovernmental review

This NOFO is not subject to Executive Order 12372, Intergovernmental Review of Federal Programs. No action is needed.

Dental Services Report

Dental Services Report : You must submit this report electronically. Complete and submit the Dental Reimbursement Program Dental Services Report in the Dental Services Report website. You'll need to request access to the website the first time you visit it by completing the registration form on the Dental Services Report website.

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Step 6: Learn What Happens After Award

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Post-award requirements and administration

Administrative and national policy requirements

There are important rules you need to know if you get an award. You must follow:

- All terms and conditions in the Notice of Award (NOA). We incorporate this NOFO by reference.
- The regulations at 2 CFR Part 200, Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards, modifications at 2 CFR Part 300, and any superseding regulations.
- The HHS Grants Policy Statement. Your NOA will reference this document. If there are any exceptions to the GPS, they'll be listed in your NOA.
- All federal statutes and regulations relevant to federal financial assistance, including those highlighted in HHS Grants Policy Statement, Appendix D: HHS Administrative and National Policy Requirements.
- The requirements for performance management in 2 CFR 200.301.
- All anti-discrimination laws: By applying for or accepting federal funds from HHS, you certify compliance with all federal antidiscrimination laws and these requirements. Complying with those laws is a material condition of receiving federal funding streams. You are responsible for ensuring subrecipients, contractors, and partners also comply.
- Any applicable statutory provisions.
- The Assurances (standard certification and representations) included in the annual SAM registration.

Required Alignment with HRSA Mission and Strategic Priorities

Recipients must use funds awarded under this NOFO to implement program goals or agency priorities in accordance with the HRSA vision, mission, core values, and strategic priorities, where authorized by law.

In administering programs under this and all funding announcements, HRSA prioritizes:

- **Evidence-based healthcare:** Funding activities supported by rigorous scientific evidence, particularly for programs serving children and adolescents, where HRSA is committed to approaches that reflect the highest standards of clinical care and child safety.

- **Biological and physiological integrity:** Recognizing the relevance of biological sex to health outcomes, HRSA encourages applicants to account for sex-based health factors in program design, data collection, and service delivery where scientifically appropriate.

HRSA will implement these priorities consistent with applicable laws, regulations, court orders, and all required administrative procedures. Applicants are encouraged to describe how their proposed programs align with these priorities in their project narratives.

Funded activities must advance HRSA's vision of protecting and improving the health and well-being of Americans. The particular focus is on those who are medically vulnerable or live in areas with limited access to care. HRSA's duty is to serve

wisely, effectively, and with measurable results that justify every taxpayer dollar invested.

Consistent with HRSA's priorities, in carrying out any project funded under this NOFO, the recipient must adhere to the following principles, where they are consistent with the authority and scope of the award and its activities:

- **Gold standard science:** Design and deliver services using gold standard evidence-based and evidence-informed approaches, establish measurable performance goals, and use data to monitor outcomes and drive continuous improvement.
- **Program integrity and fiscal stewardship:** Recipients must:
  - Administer funds in accordance with all applicable federal statutes, regulations, and award conditions.
  - Maintain strong internal controls.
  - Prevent waste, fraud, and abuse.
- **Partnership and local leadership:** Coordinate with state, tribal, territorial, local, and community partners, as appropriate, and tailor services to meet community-identified needs while respecting local decision-making authority.

Recipients must manage any project awarded under this NOFO in accordance with the following objectives in programs authorized to advance them:

Make America Healthy Again (MAHA): HRSA prioritizes the health and well-being of all Americans by supporting common-sense, evidence-based health policies that promote:

- Personal responsibility.
- Strong families and communities.
- Proper nutrition.
- The prevention and management of chronic disease, while ensuring access to high-quality, affordable physical and mental health care.

Child protections, biological integrity, parental rights, and lawful use of funds: HRSA prioritizes safeguarding children's health and safety by:

- Not supporting medical interventions for gender dysphoria in minors that lack a strong evidence base.
- Applying sex-based definitions grounded in biological reality.
- Supporting parental authority, transparency, and choice in education, including school-based health centers that respect parental rights and religious upbringing.
- Ensuring taxpayer funds are not used to promote or support elective abortions, consistent with federal law and the Hyde Amendment.

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Advancing evidence-based, merit-driven, and ethically grounded health care: HRSA will prioritize unbiased, transparent science; merit-based workforce opportunities; and programs that demonstrate measurable outcomes, while deprioritizing organizations with:

- Conflicts of interest.
- "Harm reduction" models.
- Housing-first approaches.
- Activities that facilitate illegal drug use or unsafe medical practices.

Promoting public safety, lawful use of federal funds, and national health priorities: To the extent permitted by law, HRSA will align funding with administration priorities by:

- Supporting ending the HIV epidemic through authorized, evidence-based care.
- Reserving benefits for eligible individuals.
- Discouraging illegal immigration and unsafe community practices.
- Prioritizing recipients that enforce public safety, address serious mental illness and substance use through treatment and recovery, and reduce homelessness responsibly.

To the extent allowable by law, under awards, HRSA will give priority to states and municipalities for programs to:

- Enforce prohibitions on open illicit drug use.
- Enforce prohibitions on urban camping and loitering.
- Enforce prohibitions on urban squatting.
- Enforce, and where necessary, adopt, standards that address individuals who are a danger to themselves or others and suffer from serious mental illness or substance use disorder, or who are living on the streets and cannot care for themselves. The approach must be through assisted outpatient treatment or by moving them into treatment centers or other appropriate facilities through civil commitment or other available means, to the maximum extent permitted by law.

HRSA will implement these priorities consistent with applicable laws, regulations, court orders, and any required procedures.

The recipient must demonstrate ongoing compliance with these priorities, in all programs that are authorized to advance them, through program design, implementation, reporting, and evaluation.

Failure to meaningfully align funded activities with the applicable requirements may result in corrective action, additional reporting requirements, or other actions consistent with federal grant regulations at 2 CFR. part 200 and the terms and

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conditions of this award. This includes termination under 2 CFR. 200.340(a)(4) if an award no longer effectuates the program goals or agency priorities.

Cybersecurity

If awarded, you must develop plans and procedures, modeled after the NIST Cybersecurity framework, to protect HHS systems and data. See details here.

Health IT

Successful applicants under this NOFO agree that:

Where award funding involves:	Recipients and subrecipients are required to:
Implementing, acquiring, or upgrading health IT for activities funded by any entity.	Use health IT that meets standards and implementation specifications adopted in 45 CFR 170, Subpart B, if such standards and implementation specifications can support the activity. Visit to 45 CFR 170, Subpart B learn more.
Implementing, acquiring, or upgrading health IT for activities by eligible clinicians in ambulatory settings, or hospitals, eligible under Sections 4101, 4102, and 4201 of the HITECH Act.	Use health IT certified under the ONC Health IT Certification Program if certified technology can support the activity. Visit the Certification of Health IT site to learn more.

If standards and implementation specifications adopted in 45 CFR part 170, Subpart B cannot support the activity, recipients and subrecipients are encouraged to use health IT that meets non-proprietary standards and implementation specifications developed by consensus-based standards development organizations. This may include standards identified in the ONC Interoperability Standards Advisory.

Reporting

If you are funded, you will have to follow the reporting requirements in “reporting” section of the Application Guide. The NOA will provide specific details.

You must also follow these program-specific reporting requirements:

- Progress reports, Federal Financial Report, and the final report noted under Section 6 of HRSA’s SF 424 Application Guide are not required for DRP.

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Agency contacts

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HRSA contact center

Open Monday to Friday, 7 a.m. to 8 p.m. ET, except for federal holidays.
Call: 877-464-4772 / 877-Go4-HRSA
TTY: 877-897-9910

Electronic Handbooks Contact Center

Help with systems

Grants.gov

Grants.gov provides 24/7 support. You can call 800-518-4726, search the Grants.gov Knowledge Base, or email Grants.gov for support. Hold on to your ticket number.

SAM.gov

If you need help, you can call 866-606-8220 or live chat with the Federal Service Desk.

Helpful websites

- Application Guide
- HRSA Grants page
- HHS Tips for Preparing Grant Proposals
- Frequently Asked Questions
- Applicant Training

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Appendix

Dental Services Report

Instructions

For instructions on completing the report, see reporting requirements on our website under “Dental Services Report.”

We will only accept actual counts of people with HIV who received oral health care services from your institution or program as the basis of your application for DRP funding.

- **Funding and payment coverage:** You should only report direct reimbursements from third party payers (public and private) as payment for services provided in Section 2 Tabs 1 & 2. You should not report funding from the RWHAP or other federal grant programs as reimbursements in these items.
- **Unreimbursed costs:** The total unreimbursed costs of oral health care provided to people with HIV from July 1, 2024, through June 30, 2025, that are entered in fields 18a and 18g of the SF-424 Application for Federal Assistance must match the amount reported in Section 4 Tab 2 on the Dental Reimbursement Program Dental Services Report. We may verify the unreimbursed costs listed on the DSR and SF-424 application for Federal Assistance if there are differences. ***If these amounts do not match, we may deem your application ineligible.**
- **Narratives:** Please include narrative responses in Section 4 Tab 3, not to exceed one page in length for each item. Your responses will better inform us about your institution or program; your collaborations in the larger community; your training of students, residents, and providers; and other accomplishments. Your responses will also help us target technical assistance activities, document the value of funds expended, and demonstrate the importance of continued RWHAP funding for oral health care.

EXHIBIT E

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV



Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Antiretroviral Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed (insert date) [insert page number, table number, etc., if applicable].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinicalinfo website (https://clinicalinfo.hiv.gov/).

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What's New in the Guidelines

Updated: September 12, 2024
Reviewed: September 12, 2024

These guidelines were updated by the U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) based on key new clinical evidence on the use of antiretroviral therapy (ART) for the treatment of people with HIV.

New Section Added to the Guidelines

Transplantation in People With HIV

This new section has been added to provide guidance on ART management in people with HIV who are candidates or recipients of solid organ and hematopoietic cell transplants. The Panel emphasizes the importance of maintaining HIV viral suppression before and after a transplant. The addition of immunosuppressive therapy and prophylaxis against opportunistic infections to ART increases pill burden and the potential for drug–drug interactions and adverse effects. Because of the complexities of medical management, the Panel recommends that people with HIV who require transplantation be managed by a multidisciplinary team before, during, and after transplant **(AIII).**

Key Revisions to the Guidelines

What to Start: Initial Combination Antiretroviral Regimens for People With HIV

Several changes have been made to the Panel's recommendations for initial ART regimens for people with HIV. The regimens recommended by the Panel as initial ART for people with HIV include those that have demonstrated clinical efficacy, have a high barrier to resistance, are well tolerated, and can be given as once-daily therapy. The Panel made the following changes to the recommended initial ART regimens:

- Dolutegravir (DTG)/abacavir/lamivudine (3TC) has been changed from one of the Recommended Initial Regimens for Most People With HIV (Table 6a) to a regimen recommended as part of Other Initial Antiretroviral Regimens for Certain Clinical Scenarios (Table 6b) due to the need for HLA-B*5701 testing before initiating therapy, the potential increase in the risk of cardiovascular events, and the availability of other options for initial therapy.
- Several antiretroviral (ARV) regimens are no longer recommended as initial therapy due to higher pill burdens, more adverse effects, or a lower barrier to resistance than other ART regimens recommended by the Panel. These regimens include the following:
  - Elvitegravir/cobicistat and raltegravir-based regimens
  - Boosted atazanavir-based regimens
  - Efavirenz-based regimens
  - Rilpivirine (RPV)/tenofovir disoproxil fumarate/emtricitabine (FTC) regimens

Virologic Failure

Updates made to the Virologic Failure section include the following:

- For people who experience virologic failure while on their first ARV regimen of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs), a salvage regimen of DTG plus boosted darunavir can be used **(AI)**. This recommendation is based on data from the D^2EFT trial, a large randomized controlled trial comparing this regimen to a regimen of DTG plus two NRTIs.
- Some people with HIV cannot reach or maintain viral suppression on oral ART despite intensive adherence support. A complete regimen of long-acting injectable cabotegravir and rilpivirine (LA CAB/RPV) has been used in this population with some success, although long-term efficacy data are limited. Based on very limited data, the Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to CAB or RPV, and with shared decision-making between providers and people with HIV **(CIII).** The Panel notes that people with HIV and their providers must be aware of the significant risk of developing resistance to NNRTIs, and particularly integrase strand transfer inhibitors (INSTIs) if virologic failure occurs on LA CAB/RPV. Such resistance may limit future treatment options and may also lead to HIV transmission.

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

Updates made to the Optimizing Antiretroviral Therapy in the Setting of Viral Suppression section include the following:

- Because more people with HIV are switched to regimens that do not include NRTIs or only include 3TC, the Panel has expanded the guidance to emphasize the importance of keeping regimens that contain hepatitis B virus (HBV)–active drugs for people with HBV/HIV coinfection. For people with no known history of HBV infection, the Panel noted the need to screen for HBV before initiating NRTI-sparing (or limited) regimens.
- The discussion of LA CAB/RPV as a switch strategy with data from additional clinical trials and information on the use of this regimen in people who have challenges with adherence to oral ART.
- The Panel expanded on the discussion of clinical trial data on switch strategies in people with limited or extensive drug resistance.

HIV and the Older Person

Updates made to the HIV and the Older Person section include the following:

- A new subsection on HIV and Immunologic Aging.
- Expanded discussions on non-AIDS complications among older people with HIV.
- A discussion on atherosclerotic cardiovascular disease in older people with HIV and the recent recommendation for the use of statins in people with HIV (see Statin Therapy in People With HIV).

Substance Use Disorders and HIV

Updates made to the Substance Use Disorders and HIV section include the following:

- A new subsection on Substance Use and Unstable Housing that includes discussion of the impact of unstable housing on the HIV care continuum and adherence to ART.

- An expanded discussion on considerations when using LA CAB/RPV in people with HIV and substance use disorder.
- A new subsection that includes a discussion on xylazine, an adulterant that may be added to opioids, such as fentanyl. The Panel notes that xylazine is a cytochrome P450 (CYP) 3A4 substrate; thus, its half-life may be prolonged in the presence of CYP3A4 inhibitors, such as ritonavir or cobicistat, further increasing the risk of overdose.

Transgender People With HIV

Updates made to the Transgender People With HIV section include the following:

- An update on the epidemiology of transgender people with HIV based on recent data from national surveys and Centers for Disease Control and Prevention (CDC) surveillance reports.
- An expanded discussion on barriers that transgender adults and adolescents with HIV may face in accessing care and maintaining HIV suppression.
- A new table that lists the most commonly used gender-affirming hormone therapies (GAHT).
- Updates to the drug–drug interaction table for interactions between GAHT and ARV drugs to include newer ARV drugs used in clinical practice.
- The Panel expanded discussion on cardiovascular disease risk in transgender people with HIV who use GAHT.

Hepatitis B Virus/HIV Coinfection

Updates made to the Hepatitis B Virus/HIV Coinfection section include the following:

- The Panel no longer recommends pegylated interferon as a therapy for the treatment of HBV in people with HIV **(AIII).** Pegylated interferon should only be considered in rare cases and with consultation with an expert in HBV**.**
- The Panel noted that approximately 4% of people with HBV/HIV coinfection are also found to have hepatitis D virus (HDV) in serologic testing. Because HBV/HDV coinfection is associated with serious liver complications, experts recommend screening for HDV in people with HBV/HIV coinfection.
- The Panel emphasizes that for people with HBV/HIV coinfection who are planning to switch to an NRTI-sparing regimen, ARV drugs that are active against HIV should be continued **(AII)** or another anti-HBV drug (i.e., entecavir) should be initiated **(AII).**
- Due to increased interest in switching people to NRTI-sparing or NRTI-limiting ARV regimens, this section stresses the importance of screening for HBV before switching to NRTI-sparing or NRTI-limiting regimens in people who are not known to have HBV infection. The Panel recommends vaccination for those found to be nonimmune to HBV and provides guidance for monitoring and managing people with prior exposure to HBV.

Tuberculosis/HIV Coinfection

Updates made to the Tuberculosis/HIV Coinfection section include the following:

- The Panel previously did not recommend the use of a DTG-based regimen for people with HIV who use a once-daily isoniazid plus rifapentine regimen for the treatment of latent tuberculosis infection. Based on data from a recently published pharmacokinetics (PK) study, the Panel now recommends that—
    - For a person with virologic suppression while on a once-daily DTG 50 mg regimen, the DTG dose should be increased to 50 mg twice daily throughout the course of once-daily isoniazid plus rifapentine for 1 month (1HP), continuing DTG twice daily for 14 days after 1HP completion before switching back to once-daily DTG dosing **(AII).**
- The subsection on Drug Interaction Considerations has been updated to indicate that rifamycins are not recommended for use with the long-acting injectable drugs CAB, RPV, or lenacapavir.

Adherence to the Continuum of Care Section

Updates made to the Adherence to the Continuum of Care section include the following:

- The section emphasizes that addressing social determinants of health is essential for enhancing adherence throughout the HIV continuum of care.
- A new subsection has been added to discuss the importance of guiding individuals with HIV through transitions between different health care systems to ensure continuity of care.
- The subsection on the use of LA CAB/RPV in people with viremia and ongoing challenges to oral ART adherence or retention in care has been expanded to incorporate recommendations from the Virologic Failure section of the guidelines.

Drug–Drug Interactions

Tables 24a through 24g have been updated with new PK data on interactions between ARV drugs and other drugs, including drugs that were approved by the U.S. Food and Drug Administration in the past 3 years and that may have interactions with ARV drugs.

Other Updates

Minor updates have been made to the following sections of the guidelines:

- Drug-Resistance Testing
- Early (Acute and Recent) HIV Infection
- Women With HIV
- Cost Considerations and Antiretroviral Therapy
- Appendix B, Table 12

Sections Removed From the Guidelines

- Antiretroviral Components or Regimens Not Recommended as Initial Therapy
- What Not to Use

Panel Roster

Updated: September 12, 2024
Reviewed: September 12, 2024

Members and Consultants of the U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents

These guidelines were developed by the U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (a working group of the National Institutes of Health Office of AIDS Research Advisory Council).

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Financial Disclosure

Updated: September 12, 2024
Reviewed: September 12, 2024

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Financial Disclosure for Companies Related to HIV Treatment or Diagnostics for the Period of April 1, 2023, to March 31, 2024

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Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Financial Disclosure for Companies Related to HIV Treatment or Diagnostics for the Period of April 1, 2023, to March 31, 2024 (continued)

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Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Financial Disclosure for Companies Related to HIV Treatment or Diagnostics for the Period of April 1, 2023, to March 31, 2024 (continued)

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Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Financial Disclosure for Companies Related to HIV Treatment or Diagnostics for the Period of April 1, 2023, to March 31, 2024 (continued)

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Key: C = Co-chair; CC = Cardiology Consultant; CTC = Consultant for Transgender Care; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; HC = HIV-2 Consultant; M = Member; N/A = not applicable; PC = Pharmacology Consultant; TC = Transplant Consultant; UCSF = University of California, San Francisco

Introduction

Updated: September 21, 2022
Reviewed: September 21, 2022

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition, with life expectancy approaching that for people without HIV.[1,2] ART is also highly effective at preventing sexual transmission of HIV in patients who have adequately suppressed viral loads.[3-5] Lack of viral load suppression is mostly due to undiagnosed HIV infection and failure to link or retain patients with HIV in care.

The U.S. Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The Panel's primary goal is to provide HIV care practitioners with recommendations that are based on current knowledge of the antiretroviral (ARV) drugs that are used to treat adults and adolescents with HIV in the United States. The Panel reviews new evidence and updates recommendations when needed. These guidelines include recommendations on baseline laboratory evaluations, treatment goals, benefits of ART and considerations when initiating therapy, choice of the initial regimen for ART-naive people with HIV, ARV drugs or combinations to avoid, management of treatment failure, optimizing ARV regimens, management of adverse effects and drug interactions, and special ART-related considerations in specific populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV to provide recommendations for adolescents at different stages of growth and development. Recommendations for ARV regimens in these guidelines are most appropriate for postpubertal adolescents (i.e., those with sexual maturity ratings [SMR] of 4 and 5). Clinicians should follow recommendations in the Pediatric Antiretroviral Guidelines when initiating ART in adolescents with an SMR of 3 or lower. For recommendations related to pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention.[6]

These guidelines represent current knowledge regarding the use of ARV drugs. Because the science of HIV evolves rapidly, the availability of new agents and new clinical data may change therapeutic options and preferences. Information included in these guidelines may not always be consistent with approved labeling for the specific drugs or indications, and the use of the terms "safe" and "effective" may not be synonymous with the U.S. Food and Drug Administration–defined legal standards for drug approval. The Panel frequently updates the guidelines (current and archived versions of the guidelines are available on the Clinical Info website). However, updates to the guidelines may not keep pace with the release of new data, and the guidelines cannot offer guidance on care for all patients. Patient management decisions should be based on clinical judgement and attention to unique patient circumstances.

The Panel recognizes the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of ART and encourages both the development of protocols and patient participation in well-designed Institutional Review Board–approved clinical trials.

HIV Expertise in Clinical Care

Several studies have demonstrated that overall outcomes in patients with HIV are better when care is delivered by clinicians with HIV expertise (e.g., those who have cared for a large group of patients with HIV),[7-11] reflecting the complexity of HIV transmission and its treatment. Appropriate training, continuing education, and clinical experience are all components of optimal care. Providers who do not have this requisite training and experience should consult HIV experts when needed.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents for the treatment of HIV in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 50 voting members who have expertise in HIV care and research and includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Health Resource and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are nongovernmental scientific members. The Panel also includes four to five community members with knowledge of HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open call for nominations. Each member serves on the Panel for a 4-year term, with an option for reappointment for an additional term. See the Panel Roster for a list of current Panel members.
Financial disclosure	All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used to manage HIV infection. The latest version of the Financial Disclosure list is available on the Clinical Info website.
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are based on studies published in peer-reviewed journals or data available in FDA drug labels. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in Table 2 below
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the section's area of interest. The working groups synthesize available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Other guidelines	These guidelines focus on antiretroviral therapy (ART) for adults and adolescents with HIV. For a more detailed discussion on the use of ART in children and prepubertal adolescents (those with sexual maturity ratings of 1 to 3), clinicians should refer to the Pediatric Antiretroviral Guidelines. These guidelines also include a brief discussion on the management of persons of childbearing potential and pregnant persons. For more details on the use of ARV drugs during pregnancy, see the Perinatal Guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety or efficacy data, or other information relating to ARV drugs that may have an impact on the clinical care of people with HIV. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the Clinical Info website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the Clinical Info website.
Public comments	A 2-week public comment period follows the release of the updated guidelines on the Clinical Info website. The Panel reviews comments to determine whether additional revisions to the guidelines are indicated. The public also may submit comments to the Panel at any time at HIVinfo@NIH.gov.

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation statement includes a letter **(A**, **B**, or **C)** that represents the strength of the recommendation and a Roman numeral **(I**, **II**, or **III)** that represents the quality of the evidence that supports the recommendation (see Table 2 below).

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Weak recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

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Baseline Evaluation

Updated: September 21, 2022
Reviewed: September 21, 2022

Every patient with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of this initial evaluation are to confirm the diagnosis of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and initiate care as recommended in the HIV Medicine Association of the Infectious Diseases Society of America's (HIVMA/IDSA) Primary Care Guidance for Persons with HIV[1] and the Adult and Adolescent Opportunistic Infections Guidelines.[2] The initial evaluation also should include discussion of the benefits of antiretroviral therapy (ART) for the patient's health and to prevent HIV transmission, as well as strategies to optimize care engagement and treatment adherence **(AIII).** Information obtained in this baseline evaluation then can be used to define treatment management goals and plans. The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART at the time of diagnosis (when possible) or as soon as possible afterward to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, improve the rate of virologic suppression, and reduce HIV transmission **(AII).**

The following laboratory tests performed during initial patient visits can be used to stage HIV progression and to assist in the selection of antiretroviral (ARV) drug regimens:

- HIV antigen/antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) **(AI)**
- CD4 T lymphocyte (CD4) cell count **(AI)**
- Plasma HIV RNA (viral load) **(AI)**
- Complete blood count; chemistry profile, including glucose, blood urea nitrogen and creatinine, liver enzymes and bilirubin, urinalysis, and serologies for hepatitis A, B, and C viruses **(AIII)**
  - If random blood glucose level is abnormal, repeat fasting
- Serum lipids (if random levels are abnormal, fasting lipids should be obtained)
- HLA-B*5701 test (if abacavir is being considered) **(AI)**
- Genotypic drug-resistance testing **(AII).** Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive people should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern in people with newly diagnosed HIV or in people who acquired HIV after receipt of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), testing for mutations in the integrase gene also should be performed.
- For patients who have HIV RNA levels <1,000 copies/mL, viral amplification for drug-resistance testing should still be performed; however, it may not always be successful **(BII)** (see Drug-Resistance Testing).

In addition, other tests (including screening tests for sexually transmitted infections, opportunistic infections, and cancer) should be performed as recommended in the HIVMA/IDSA's Primary Care Guidance for Persons with HIV[1] and the Adult and Adolescent Opportunistic Infections Guidelines.[2]

Many clinics have adopted a rapid start policy to initiate ART on the day of HIV diagnosis in order to increase ART uptake and engagement in care and to accelerate the time to viral suppression. Rapid ART initiation also reduces the time during which people with newly diagnosed HIV can transmit HIV. Prior to ART initiation, HIV infection should be confirmed. HIV RNA and CD4 count also should be obtained, but results need not be available before starting ART. CD4 count will determine the need for prophylaxis for certain opportunistic infections.

- If available, results of safety testing—such as complete blood count, renal function tests, and liver enzymes—should be reviewed. If safety test results are not available, ART can still be started, but a clinician should review the results as soon as possible.
- Genotypic resistance testing for RT and PR (and INSTI resistance testing if patient has a history of CAB PrEP use or if INSTI transmission is suspected) should be obtained before ART initiation. It is not necessary to delay ART until results are available, but results should be reviewed as soon as possible in order to make adjustments to the regimen, if needed.
- Screening for viral hepatitis should be done before starting ART, and if ART initiation occurs before results are available, a regimen that has activity against hepatitis B virus should be selected.
- In patients who do not have reliable methods of contact, rapid ART may be initiated, with a plan for a return clinic visit soon after ART initiation to review test results.
- Screening for sexually transmitted infections should, ideally, occur at the initial visit, but results do not need to be available before starting ART.

For previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete ARV history (including drug-resistance testing results, if available), preferably through the review of past medical records. A complete immunization history (including for SARS-CoV-2) also should be obtained. Newly diagnosed patients also should be asked about any prior use of ARV agents for prevention of HIV infection.

People with HIV often must cope with many social, psychiatric, and medical issues that are best addressed through a patient-centered, multidisciplinary approach. The baseline evaluation should include consideration of the patient's readiness for ART, including an assessment of substance use (including tobacco use), social support, mental health, medical comorbidities, economic factors (e.g., unstable housing, food instability), medical insurance status and adequacy of coverage, and other factors that are known to impair adherence to ART and increase the risk of HIV transmission. Once evaluated, these factors should be managed accordingly. The baseline evaluation also should include a discussion of risk reduction and disclosure to sexual and/or needle-sharing partners, especially with untreated patients who are still at high risk of HIV transmission. People with HIV should be informed that maintaining a plasma HIV RNA of <200 copies/mL, including any measurable value below this threshold, with ART prevents sexual transmission of HIV to their partners **(AII).** Patients may recognize this concept as Undetectable = Untransmittable or U=U.

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Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring of People With HIV Receiving Antiretroviral Therapy

Updated: September 21, 2022
Reviewed: September 21, 2022

Several laboratory tests are important for initial evaluation of people with HIV upon entry into care. Some tests should be performed before and after initiation or modification of antiretroviral therapy (ART) to assess the virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs. Table 3 below outlines recommendations from the Panel on Antiretroviral Guidelines for Adults and Adolescents on the frequency of testing. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are used to monitor people with HIV: plasma HIV RNA (viral load) to assess level of HIV viremia and CD4+ T lymphocyte cell count (or CD4 count) to assess immune function. Standard (reverse transcriptase and protease) genotypic drug-resistance testing should be used to guide selection of an ARV regimen; if transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern or for people who acquired HIV after taking long-acting cabotegravir as pre-exposure prophylaxis, testing also should include the integrase gene (see Drug-Resistance Testing). For guidance on the choice of ARV regimens before drug-resistance testing results become available, clinicians should consult the What to Start section. A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure that occurs while a patient is receiving a CCR5 antagonist. HLA-B*5701 testing should be performed before initiation of abacavir (ABC) to reduce the risk of hypersensitivity reaction, and HLA-B*5701-positive patients should not be prescribed ABC. Patients should be screened for hepatitis B and hepatitis C virus infections before initiating ART and, if indicated, periodically after ART initiation, because treatment of these coinfections may affect the choice of ART and likelihood of drug-induced hepatotoxicity. The rationale for and utility of some of these laboratory tests are discussed in the corresponding sections of the guidelines.

Table 3. Laboratory Testing Schedule for Monitoring People With HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
HIV Antigen/ Antibody Test	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√		√[d] If CD4 count is <300 cells/mm^3	√ During the first 2 years of ART, if CD4 count is ≥ 300 cells/mm^3	√ **After 2 Years on ART with Consistently Suppressed Viral Load** *CD4 Count 300–500 cells/mm^3* • Every 12 months *CD4 Count >500 cells/mm^3* • CD4 count monitoring is optional.	√	√	√ Every 3–6 months

Table 3. Laboratory Testing Schedule for Monitoring People With HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
HIV Viral Load	√	√	√[e]	√[f]	√[f]		√	√	Repeat testing is optional.
Genotypic Resistance Testing (PR/RT Genes)[g]	√	√					√	√	√
Genotypic Resistance Testing (Integrase Genes)[g]	√ If transmitted INSTI resistance is suspected or if there is a history of CAB-LA use for PrEP	√[f] If transmitted INSTI resistance is suspected or if there is a history of INSTI use					√ If there is a history of INSTI use	√ If there is a history of INSTI use	

Table 3. Laboratory Testing Schedule for Monitoring People With HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist, or for patients with virologic failure on a CCR5 antagonist	√	
HLA-B*5701 Testing		√ If considering ABC							
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)[h,i,j]	√	In patients not immune to HBV, consider retesting if switching to a regimen that does not contain TDF or TAF.						√ Including before starting HCV DAA	

Table 3. Laboratory Testing Schedule for Monitoring People With HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
Hepatitis C Screening (HCV antibody or, if indicated, HCV RNA)[k]	√					√ Repeat HCV screening for at-risk patients[l]		√	
Basic Metabolic Panel[m,n]	√	√	√		√			√	√ Every 6–12 months
ALT, AST, Total Bilirubin	√	√	√		√			√	√ Every 6–12 months
CBC with Differential[o]	√	√		√ When monitoring CD4 count (if required by lab)	√ When monitoring CD4 count (if required by lab)	√ When no longer monitoring CD4 count		√	
Lipid Profile[p]	√		Consider 1–3 months after ARV initiation or modification			√ If normal at baseline but with CV risk		If normal at baseline, every 5 years or if clinically indicated	

Table 3. Laboratory Testing Schedule for Monitoring People With HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
Random or Fasting Glucose[q]	√	√					√	√	
Urinalysis[n,r]	√							√ E.g., in patients with CKD or DM	
Pregnancy Test[s]	√	√						√	

[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Medicine Association of the Infectious Diseases Society of America's (HIVMA/IDSA) Primary Care Guidance for Persons with HIV for other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

[b] If ART is initiated soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

[c] ART is indicated for all people with HIV and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

[d] After 2 years of consistently suppressed HIV RNA, less frequent monitoring (e.g., every 6 months) may be considered.

[e] If HIV RNA is detectable at 4–8 weeks, repeat testing every 4–8 weeks until viral load is suppressed to <50 copies/mL. Thereafter, repeat testing every 3–6 months.

[f] For patients on ART, viral load typically is measured every 3–6 months. More frequent monitoring may be considered in individuals having difficulties with ART adherence or at risk for nonadherence. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 1 year, monitoring can be extended to 6-month intervals.

[g] Standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the PR and RT genes. If transmitted INSTI resistance is a concern, or if a person has a history of INSTI use as PrEP or treatment, or a person presents with viremia while on an INSTI, providers also should test for resistance mutations in the IN gene. In ARV-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if drug-resistance testing was performed at entry into care. In

Table 3. Laboratory Testing Schedule for Monitoring People With HIV Before and After Initiation of Antiretroviral Therapy[a]

patients with virologic suppression who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; see the Drug-Resistance Testing section for a discussion of the potential limitations and benefits of proviral DNA assays in this situation. Results from prior drug-resistance testing should be considered because they can be helpful in constructing a new regimen.

[h] If a patient has HBV infection (as determined by a positive HBsAg or HBV DNA test result), TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections (see the Hepatitis B Virus/HIV Coinfection section).

[i] If HBsAg, HBsAb, and HBcAb test results are negative, HBV vaccine series should be administered. Refer to the HIVMA/IDSA's Primary Care Guidance for Persons with HIV and the Adult and Adolescent Opportunistic Infection Guidelines for detailed recommendations.[1,2]

[j] Most patients with isolated HBcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load test for confirmation. If the HBV viral load test is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If the test is negative, the patient should be vaccinated. Refer to the HIVMA/IDSA's Primary Care Guidance for Persons with HIV and the Adult and Adolescent Opportunistic Infection Guidelines for more detailed recommendations.[2]

[k] The HCV antibody test may not be adequate for screening in the setting of recent HCV infection (acquisition within the past 6 months) or advanced immunodeficiency (CD4 count <100 cells/mm^3). HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative patients with elevated ALT may need HCV RNA testing.

[l] Injection drug users, people with a history of incarceration, men with HIV who have unprotected sex with men, and people with percutaneous/parenteral exposure to blood in unregulated settings are at risk of HCV infection.

[m] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose, and Cr-based eGFR. Serum P should be monitored in patients with CKD who are on TDF-containing regimens.[3]

[n] Consult the HIVMA/IDSA's Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV for recommendations on managing patients with renal disease.[3] More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

[o] CBC with differential should be done when a CD4 count is performed. When CD4 count is no longer being monitored, the recommended frequency of CBC with differential is once a year. More frequent monitoring may be indicated for people receiving medications that potentially cause cytopenia (e.g., TMP-SMX).

[p] If random lipids are abnormal, fasting lipids should be obtained. Consult the American College of Cardiology/American Heart Association's 2018 Guideline on the Management of Blood Cholesterol for diagnosis and management of patients with dyslipidemia.[4]

[q] If random glucose is abnormal, fasting glucose should be obtained. HbA1C is no longer recommended for diagnosis of diabetes in people with HIV on ART (see the American Diabetes Association Guidelines).[5]

[r] Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

[s] For persons of childbearing potential.

Key: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CAB-LA = cabotegravir long-acting; CBC = complete blood count; CD4 = CD4 T lymphocyte; CKD = chronic kidney disease; Cl = chloride; Cr = creatinine; CV = cardiovascular; DAA = direct-acting antiviral; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; HbA1C = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO_3 = bicarbonate; HCV = hepatitis C virus; IN = integrase; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; P = phosphorus; PR = protease; PrEP = pre-exposure prophylaxis; RT = reverse transcriptase; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TMP-SMX = trimethoprim-sulfamethoxazole

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Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring

Updated: September 21, 2022
Reviewed: September 21, 2022

HIV RNA (viral load) and CD4 T lymphocyte cell (CD4) count are the two surrogate markers of antiretroviral therapy (ART) responses and HIV disease progression that have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.[1] The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART.

CD4 count provides information on the overall immune function of a person with HIV. Measurement of CD4 count is particularly useful **before** initiation of ART to establish the need for the initiation of opportunistic infection (OI) prophylaxis and to assess the urgency to initiate ART; and **after** initiation of ART to assess immunologic response and to establish the need for discontinuation of OI prophylaxis.

The management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. ART is now recommended for all patients with HIV regardless of their viral load or CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). In the past, the clinical practice supported by treatment guidelines was generally to monitor both CD4 count and viral load concurrently. However, because most patients with HIV in care now receive ART, the rationale for frequent CD4 count monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed in the following sections.

Plasma HIV-1 RNA (Viral Load) Monitoring

Viral load is the most important indicator of initial and sustained response to ART and should be measured in all patients with HIV at entry into care **(AI),** at initiation of therapy **(AI),** and on a regular basis thereafter. For those patients who choose to delay therapy or remain untreated for whatever reason, repeat viral load testing while not on ART is optional **(CIII).** Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen, because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load (see the What to Start section). Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see the HIV-2 Infection section.

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-3] Thus, viral load testing is an established surrogate marker for treatment response.[4] The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 $\log_{10}$ copies/mL change). Optimal viral suppression is defined as a confirmed HIV RNA level below the lower limit of detection of available assays (generally <20 copies/mL, depending on the assay used). After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression, known as a "blip," may occur in successfully treated patients and is not usually predictive of virologic failure.[5] Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.[6-9] These guidelines and the AIDS Clinical Trials Group (ACTG) now define

virologic failure as the inability to achieve or maintain suppression of viral replication to HIV RNA level <200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[10] (see the Virologic Failure section).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 12 weeks after ART initiation or after modification due to virologic failure; rarely, it may take longer in some patients. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART.** Plasma viral load should be measured before initiation of ART and within 4 to 8 weeks after treatment initiation **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII).**
- **In patients with viral suppression, with ART modification because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy **(AIII).** The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.
- **In patients on a stable, suppressive ARV regimen.** Viral load measurement should be repeated every 3 to 4 months **(AIII)** or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than a year, whose clinical and immunologic status is stable, and who are not at risk for inadequate adherence **(AIII).**
- **In patients with virologic failure who require a change in ARV regimen.** Plasma viral load should be measured before ART change and within 4 to 8 weeks after treatment modification **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to the new regimen. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII).** If viral suppression is not possible, repeat viral load measurement every 3 months or more frequently if indicated **(AIII).**
- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, several other factors—such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions—should be assessed. Patients who fail to achieve viral suppression should undergo drug-resistance testing to aid in the selection of an alternative ARV regimen (see the Drug-Resistance Testing and Virologic Failure sections).

CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in patients with HIV. It is also the strongest predictor of disease progression and survival according to findings from clinical trials and cohort studies.[11,12] CD4 counts are highly variable; a significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it **is not recommended (BIII).**

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all patients at entry into care **(AI).** It is the key factor in determining the need to initiate OI prophylaxis (see the Adult and Adolescent Opportunistic Infections Guidelines)[13] and the urgency to initiate ART **(AI)** (see the Initiation of Antiretroviral Therapy section). Although most OIs occur in patients with CD4 counts <200 cells/mm^3, some OIs can occur in patients with higher CD4 counts.[14]

Use of CD4 Count for Monitoring Therapeutic Response

The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the Adult and Adolescent Opportunistic Infections Guidelines).[13] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 cells/mm^3 to 150 cells/mm^3 in the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 cells/mm^3 to 100 cells/mm^3 per year until a steady state level is reached.[15] Patients who initiate therapy with a low CD4 count[16,17] or at an older age[18] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

ART is now recommended for all patients with HIV. In patients who remain untreated for whatever reason, CD4 counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for OI prophylaxis **(AIII).**

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII).** This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the Adult and Adolescent Opportunistic Infections Guidelines.[13] For patients beginning ART, CD4 count should be repeated every 3 months for the first 2 years of suppressive ART for those with CD4 counts <300 cells/mm^3 and every 6 months if CD4 count is ≥300 cells/mm^3. After 2 years of suppressive ART, CD4 count monitoring can be reduced to every 6 months for patients whose CD4 counts remain at <300 cells/mm^3 and every year for patients with CD4 counts between 300 cells/mm^3 and 500 cells/mm^3, and is optional for those with CD4 counts >500 cells/mm^3 **(BII).**

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution (i.e., CD4 count >500 cells/mm^3), the CD4 count provides limited information. Frequent testing is unnecessary, because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to <200 cells/mm^3 are rare in patients with viral suppression and CD4 counts >300 cells/mm^3.[19] Similarly, the ARTEMIS trial found that CD4 count monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[20] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 cells/mm^3 and 200 cells/mm^3.[21] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes, such as cardiovascular disease, malignancy, and death.[22] An analysis of costs associated with CD4 count monitoring in the United States estimated that reducing CD4 count monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately $10 million.[23]

For the patient on a suppressive ARV regimen whose CD4 count has consistently ranged between 300 cells/mm^3 and 500 cells/mm^3 for at least 2 years, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends CD4 count monitoring on an annual basis **(BII).** Continued CD4 count monitoring for virologically suppressed patients whose CD4 counts have been consistently >500 cells/mm^3 for at least 2 years may be considered optional **(CIII).** The CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a patient's clinical status that may decrease CD4 count and thus prompt OI prophylaxis. Examples of such changes include the appearance of new HIV-associated clinical symptoms or initiation of treatment known to reduce CD4 count (e.g., chronic corticosteroids, antineoplastic agents) **(AIII).** In patients who fail to maintain viral suppression while on ART, the Panel recommends CD4 count monitoring every 3 to 6 months **(AIII).**

Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications, chronic corticosteroids, or the presence of acute infections. Splenectomy[24,25] or coinfection with human T-lymphotropic virus type I (HTLV-1)[26] may cause misleadingly elevated CD4 counts. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.[27]

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care **(AIII)** If ART initiation is deferred, repeat before initiating ART **(AIII).** In patients not initiating ART, repeat testing is optional **(CIII).**	At entry into care **(AI)** If ART is deferred, every 3 to 6 months[a] **(AIII)**
After initiating ART	Preferably within 4 to 8 weeks after initiation of ART **(AIII);** thereafter, every 4 to 8 weeks until viral load is suppressed **(BIII).**	3 months after initiation of ART **(AIII)**
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen **(AIII).**	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 4 to 8 weeks after modification **(AIII);** thereafter, every 4 to 8 weeks until viral load is suppressed **(BIII).** If viral suppression is not possible, repeat viral load testing every 3 months or more frequently if indicated **(AIII).**	Every 3 to 6 months **(AI)**
During the first 2 years of ART	Every 3 months **(AIII)**	Every 3 months if CD4 <300 cells/mm^3 **(BII)** Every 6 months if CD4 ≥300 cells/mm^3 **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 remains <300 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII).**	Every 6 months **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently 300–500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII).**	Every 12 months **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII).**	Optional **(CIII)**
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months **(AIII)** or more frequently if clinically indicated (see Virologic Failure).	Every 3 to 6 months **(AIII)**
Change in clinical status (e.g., new HIV clinical symptom or initiation of chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months **(AIII)**	Perform CD4 count and repeat as clinically indicated[b] **(AIII)**

[a] Some experts may repeat CD4 count measurement every 3 months in patients with low baseline CD4 counts (<200–300 cells/mm^3) before ART but every 6 months in those who initiated ART at higher CD4 counts (e.g., >300 cells/mm^3).

[b] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infection, such as new HIV-associated symptoms, or initiation of treatment with medications that are known to reduce CD4 count.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; VL = viral load

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Drug-Resistance Testing

Updated: September 12, 2024
Reviewed: September 12, 2024

Panel's Recommendations

For Initial Treatment of HIV

- HIV drug-resistance testing is recommended at entry into care for people with HIV to guide the selection of the initial antiretroviral (ARV) regimen **(AII).** If antiretroviral therapy (ART) is deferred, repeat testing may be considered at the time of ART initiation **(CIII).**
- The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends genotypic, rather than phenotypic, testing as the preferred resistance testing to guide therapy in ARV-naive people **(AIII).**
- In people with early (acute and recent) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported **(AIII).**
- Standard genotypic drug-resistance testing in ARV-naive people involves testing for mutations in the reverse transcriptase and protease genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is suspected, if the person has ever used long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis, or if the person has ever received an INSTI-based regimen for post-exposure prophylaxis, providers should ensure that genotypic resistance testing also includes the integrase gene **(AIII).**

For Antiretroviral Therapy–Experienced People

- HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ARV regimens in—
  - People with virologic failure and HIV RNA levels >200 copies/mL (**AI** for >1,000 copies/mL**, AIII** for 501–1,000 copies/mL**, CIII** for confirmed HIV RNA 201–500 copies/mL). For people with confirmed HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered.
  - People with suboptimal viral load reduction **(AII).**
- Reverse transcriptase and protease genotypic resistance testing should be performed on people with virologic failure. Integrase resistance testing should be performed on individuals who have virologic failure and have a history of prior use of an INSTI (for prevention or treatment) or are currently receiving an INSTI-based regimen **(AII).**
- For people taking a non–long-acting ARV regimen, drug-resistance testing in the setting of virologic failure should be performed while the person is still taking their ARV regimen or, if that is not possible, within 4 weeks after discontinuing their ARV regimen **(AII).** If more than 4 weeks have elapsed since the non–long-acting agents have been discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously selected resistance mutations can be missed due to lack of drug-selective pressure **(CIII).**
- For people who previously received long-acting cabotegravir and rilpivirine (LA CAB/RPV) and present with virologic failure, resistance testing (including INSTI genotypic testing) should be performed regardless of the time since the last dose of LA CAB/RPV **(AIII).**
- Genotypic testing is preferred over phenotypic-resistance testing to guide therapy in people with suboptimal virologic response or virologic failure while on first- or second-line regimens and in people in whom resistance mutation patterns are known or not expected to be complex **(AII).**
- The addition of phenotypic to genotypic resistance testing is recommended for people with known or suspected complex drug-resistance mutation patterns **(BIII).**
- All prior and current drug-resistance test results, when available, should be reviewed and considered when constructing a new regimen **(AIII).**

• When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Genotypic and Phenotypic-Resistance Assays

Genotypic and phenotypic-resistance assays are used to assess viral strains and select treatment strategies. These assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs). In some circumstances, INSTI-resistance tests may need to be ordered separately, and clinicians should check this with the testing laboratory. INSTI-resistance testing is particularly important in people who experience virologic failure while taking an INSTI-containing regimen or in those with prior use of injectable long-acting cabotegravir (CAB-LA) (either for treatment of HIV or as pre-exposure prophylaxis [PrEP]). Testing for fusion inhibitor resistance can be ordered separately when needed. There is currently no commercially available resistance test for the CD4 T lymphocyte post-attachment inhibitor ibalizumab, the gp120 attachment inhibitor fostemsavir, or the capsid inhibitor lenacapavir. For a description of co-receptor tropism testing, see Co-Receptor Tropism Assays.

Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes; in general, these assays require a plasma viral load of at least 500 to 1,000 copies/mL. Most genotypic assays involve conventional Sanger sequencing of the reverse transcriptase (RT), protease (PR), and integrase (IN) genes of circulating RNA in plasma to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the gp41 (envelope) gene associated with resistance to the fusion inhibitor enfuvirtide is also commercially available. Genotypic assays can be performed rapidly, and results are available within 1 to 2 weeks of sample collection. Interpreting these test results requires knowledge of the mutations selected by different antiretroviral (ARV) drugs and of the potential for cross-resistance to other drugs conferred by certain mutations. The International AIDS Society–USA maintains an updated list of significant resistance-associated mutations in the RT, PR, IN, and envelope genes. The Stanford University HIV Drug Resistance Database also provides helpful guidance for interpreting genotypic resistance test results.[1] Various additional tools are available to assist providers in interpreting genotypic test results.[2-5] Clinical trials have demonstrated that consulting with specialists in HIV drug resistance improves virologic outcomes.[6] Clinicians are thus encouraged to consult a specialist to interpret genotypic test results and design new, optimal ARV regimens.

A next-generation sequencing genotypic resistance assay that analyzes HIV-1 proviral DNA in host cells is now commercially available. This test aims to detect archived resistance mutations in people with HIV RNA below the limit of detection or with low-level viremia.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT, PR, and, more recently, IN and envelope gene sequences derived from a person's plasma HIV

RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express that person's HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with the replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration [IC_{50}]) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated phenotypic assays that can produce results in 2 to 3 weeks are commercially available, but they cost more to perform than genotypic assays. In addition, interpreting phenotypic assay results can be complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) associated with drug failure, although clinically significant fold increase cutoffs have been described for some drugs.[7-11] Again, consulting with a specialist to interpret test results can be helpful.

Limitations of Genotypic and Phenotypic Assays

Limitations of both genotypic and phenotypic assays include lack of uniform quality assurance testing for all available assays, relatively high cost, and insensitivity to minor viral species. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population will probably not be detected by commercially available assays. This limitation is important to note because a wild-type virus often re-emerges as the predominant population in the plasma after discontinuation of drugs that exert selective pressure on drug-resistant populations. As a consequence, the proportion of virus with resistance mutations can decrease to below the 10% to 20% threshold.[12-14] In the case of some oral ARV drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. However, with injectable agents that have prolonged half-lives (e.g., long-acting cabotegravir and rilpivirine [LA CAB/RPV]), drug pressure may persist for prolonged periods. Prospective studies have demonstrated that despite plasma reversion, reinitiating the same ARV agents (or those with similar resistance pathways) often leads to early treatment failure; the virus responsible for this failure is derived from a previously archived resistant virus.[15] Therefore, for people taking a non–long-acting ARV regimen, drug-resistance testing in the setting of virologic failure should be performed while the person is still taking their ARV regimen or, if that is not possible, within 4 weeks after discontinuing their ARV regimen **(AII).** If more than 4 weeks have elapsed since the non–long-acting agents were discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously selected resistance mutations can be missed due to lack of drug-selective pressure **(CIII).** Given the long half-lives of the long-acting injectable ARV drugs, resistance testing (including testing for resistance to INSTIs) should be performed in all people who have experienced virologic failure on a regimen of LA CAB/RPV or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation **(AIII).** However, the absence of detectable resistance in people not currently on antiretroviral therapy (ART) must be interpreted with caution when designing subsequent ARV regimens. Importantly, in addition to considering prior ART history, prior genotypic- or phenotypic-resistance test results should be obtained from old records when possible. Because the most current drug-resistance test may not be able to detect resistance mutations that were previously detected, these prior test results are clinically important and should be reviewed and considered when designing a new ARV regimen **(AIII).**

A next-generation sequencing genotypic assay that analyzes HIV-1 proviral DNA may provide additional information on drug resistance in people with low levels of plasma HIV RNA or in people whose levels are below the limit of detection **(CIII).** However, these assays might miss some or all

previous drug-resistance mutations, and they should be interpreted with caution. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Clinical Practice

Note: See Table 5 below for recommendations for the use of drug resistance assays.

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial ART.[16-19] The risk of acquiring drug-resistant virus is related to the prevalence of drug resistance in people with HIV who engage in activities that may result in HIV transmission within a given community. The prevalence of resistance and mutations by ARV drug class depends upon the population being studied (e.g., people with previous ARV exposure versus ARV-naive people), geography, and ARV class available in the region.[20] Pre-existing HIV drug resistance before initiation of ART is recognized as an issue for both high- and low-income countries. The prevalence of transmitted drug resistance (TDR) in high-income countries ranges from 9% to 14% and varies by country.[21-23] Pre-treatment drug resistance—which includes people exposed to ARVs prior to initiating first-line therapy (e.g., for PrEP or for the prevention of perinatal transmission), as defined by the World Health Organization—exceeds 10% in many countries.[20] In most TDR surveys, NNRTI resistance and NRTI resistance are the most common mutation class types detected, followed by PI- and INSTI-resistance mutations, respectively.[21-23]

Resistance testing is recommended to guide therapy selection to optimize virologic response in all people starting ART **(AII).** A genotypic assay is preferred for this purpose **(AIII).** In early (acute and recent) HIV infection, in pregnant people with HIV, or in people willing and able to initiate ART on the day or soon after HIV diagnosis, treatment initiation should not be delayed pending resistance testing results. Once results are reported, the regimen can be modified if warranted (see Early [Acute and Recent] HIV Infection) **(AIII).** In the absence of ART, resistant viruses may decline over time to less than the detection limit of standard resistance tests. However, when ART is eventually initiated, even low levels of resistant viruses may still increase the risk of treatment failure.[24-26] Therefore, if ART is deferred, resistance testing should still be performed at the time of entry into care to optimize the chance of capturing transmitted resistance **(AIII).** In this situation, the genotypic resistance test result should be used for regimen selection in the future when the person begins ART. If a person received CAB-LA as part of ART or PrEP, genotypic resistance testing should include the IN gene.

The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure. It is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier.[27-29] Though no prospective trial has directly addressed whether drug-resistance testing before initiation of therapy confers benefit in this population, data from several studies, including one prospective clinical trial, suggest that virologic responses in people with baseline resistance mutations are suboptimal.[16-19,30-34] In addition, an analysis of early RT and PR genotypic resistance testing in ARV-naive people suggests that baseline testing in this population is cost-effective and should be performed.[35] Therefore, resistance testing in people with chronic HIV is recommended at the time of entry into HIV care **(AII).**

Although no definitive prospective data exist to support the choice of one type of resistance testing over another, genotypic testing is generally preferred over phenotypic testing because of lower cost,

faster turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and easier interpretation of test results **(AIII).** If therapy is deferred, repeat testing shortly before initiating ART may be considered, because the person may have acquired drug-resistant virus (i.e., superinfection) **(CIII).**[36] Standard genotypic drug-resistance testing in ARV-naive people involves testing for mutations in the RT and PR genes. Although reports of transmission of INSTI-resistant virus are rare, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus also may increase. The prior use of CAB-LA for PrEP also may increase the risk of INSTI resistance at the time of HIV diagnosis. When INSTI resistance is possible, providers should supplement standard, baseline, genotypic resistance testing with genotypic testing of the IN gene, which may need to be ordered separately **(AIII).**

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA in host cells can be considered in people with baseline HIV RNA <1,000 copies/mL or when conventional HIV RNA drug-resistance testing is unsuccessful **(CIII).** As outlined above, the results should be interpreted with caution, as this assay might miss some or all previously existing drug-resistance mutations.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are important tools to inform treatment decisions for people who experience virologic failure while on ART. Several prospective studies have assessed the utility of resistance testing to guide ARV drug selection in people who experience virologic failure. These studies have involved genotypic assays, phenotypic assays, or both.[6,37-43] In general, these studies have found that changes in therapy based on resistance test results produce better early virologic response to salvage regimens than regimen changes guided only by clinical judgment.

In addition, one observational cohort study found that the use of genotypic drug-resistance testing in ART-experienced people with detectable plasma HIV RNA was independently associated with improved survival.[44] Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV regimens because of virologic failure in people with HIV RNA >200 copies/mL (**AI** for >1,000 copies/mL, **AIII** for 501 to 1,000 copies/mL, **CIII** for confirmed HIV RNA 201 to 500 copies/mL) (see Virologic Failure). In people with HIV RNA >200 copies/mL but <500 copies/mL, testing may be difficult to obtain outside of a research setting but still should be considered. Conventional drug-resistance testing in people with plasma viral loads ≤200 copies/mL **is not recommended** because there are unclear benefits and drug-resistance assays cannot be consistently performed at very low HIV RNA levels **(AIII).**

Resistance testing can also help to guide treatment decisions for people with HIV who have suboptimal viral load reduction **(AII).** Virologic failure in the setting of ART is, for certain people with HIV, associated with resistance to only one component of the regimen.[45-47] In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

Genotyping is preferred for resistance testing in people with HIV who experience virologic failure or suboptimal viral load reduction while on a first or second ARV drug regimen and in people for whom resistance mutation patterns are known or not expected to be complex (i.e., mutations that are straightforward, usually limited in number, or those that have clear significance) **(AII).** Often in these situations, the mutation patterns detected can be interpreted by algorithms used to predict the impact of subsequent regimens on virologic response. For people with HIV who have extensive treatment

history, complex mutational patterns may occur. In such situations, the interpretation of complex genotypes and the impact of the mutation pattern on subsequent treatment regimens can be challenging. For these individuals, phenotypic-resistance testing may provide additional helpful information **(BIII).** Rather than only predicting the impact of the detected mutations, these assays can measure *in vitro* the actual fold change in drug susceptibility, as well as the actual impact of mutation combinations and interactions on each drug under consideration.

When compared with phenotypic testing, genotypic testing costs less to perform and has a faster turnaround time and greater sensitivity for detecting mixtures of wild-type and resistant virus. In addition, observations show that genotypic and phenotypic assays are comparable predictors of virologic response to subsequent ARV regimens.[48] In people with HIV who experience virologic failure while on INSTI-based regimens or in those with prior INSTI exposure, including to CAB-LA for HIV treatment or prevention, testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII).** In this circumstance, clinicians should confirm that, when they order a resistance test, their laboratory is testing for INSTI resistance in addition to NNRTI, NRTI, and PI resistance. If INSTI-resistance testing needs to be ordered separately (as is the case in some laboratories), clinicians should request this assay in addition to standard drug-resistance testing. The addition of phenotypic to genotypic testing is generally indicated for people with known or suspected complex drug-resistance mutation patterns **(BIII).**

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for people with HIV who are experiencing treatment failure and for whom conventional HIV RNA genotypic drug-resistance testing is unsuccessful or unavailable due to low HIV RNA levels **(CIII).** As outlined above, results should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-Receptor Tropism Assays).

Use of HIV Proviral DNA Resistance Assays for Optimizing Antiretroviral Regimen in People With Viral Suppression

In the past decade, simpler, more potent, and better-tolerated ARV drugs have become available, and new ARV drugs will likely continue to emerge. Switching individual or multiple ARV drugs in a regimen is sometimes considered for people with HIV with suppressed viral load to simplify a regimen, avoid drug interactions or toxicity, or for other reasons. If a person's viral load is suppressed, standard drug-resistance testing will not be successful.

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for people with viral suppression, particularly if complex or semi-complex pre-existing resistance is suspected. In individuals who have experienced no prior virologic failures and who are on their first or second regimen, or who have genotypic testing results from when they had prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide additional useful information. However, in individuals who have experienced multiple prior failures, have a prolonged history of prior ARV regimens, or for whom prior genotypic resistance test results are not available, it may be appropriate to utilize proviral DNA genotypic testing **(CIII).** When such testing is obtained, results should be combined with all prior genotypic and phenotypic test results to construct a cumulative genotype, which incorporates all current and previously detected drug-resistance

mutations. Results from proviral DNA genotypes should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.[49,50] The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Pregnancy

In pregnancy, the goal of ART is to rapidly and maximally reduce plasma HIV RNA in order to provide optimal therapy for the pregnant person and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant people with HIV before initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI).** Phenotypic testing in those found to have complex drug-resistance mutation patterns may provide additional information **(BIII).** Optimal prevention of perinatal transmission requires prompt initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
In Early (Acute and Recent) HIV Drug-resistance testing is recommended **(AII).** A genotypic assay is generally preferred **(AIII).** Treatment should not be delayed while awaiting resistance testing results **(AIII).** See Early (Acute and Recent) HIV Infection for discussion on ART selection.	Drug-resistance testing can determine whether drug-resistant virus was transmitted or acquired while using PrEP. The initial ARV regimen can be modified, if necessary, once resistance test results are available. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat genotypic resistance testing may be considered when therapy is initiated **(CIII).** A genotypic assay is preferred **(AIII).**	Repeat testing when ART is initiated may be considered because the person may have acquired a drug-resistant virus (i.e., superinfection).
Before ART Initiation in People With Chronic HIV Drug-resistance testing is recommended at entry into HIV care to guide the selection of initial ART **(AII).** A genotypic assay is generally preferred **(AIII).** Treatment should not be delayed while awaiting resistance testing results **(AIII).**	Transmitted HIV with baseline resistance to at least one drug has been reported, and suboptimal virologic responses may be seen in people with baseline resistance mutations to ARVs in the prescribed regimen. Some drug-resistance mutations can remain detectable for years in untreated people with chronic HIV.
If transmitted or acquired INSTI resistance (including among people who had received INSTI for post-exposure prophylaxis) is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay, which may need to be ordered separately **(AIII).** Given the prolonged half-life of CAB-LA, INSTI-resistance testing should be considered in all people with HIV who previously received CAB-LA for PrEP, regardless of the time since drug discontinuation **(AIII).** See What to Start for discussion on ART selection.	Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI-resistance tests need to be ordered separately (clinicians should check with the testing laboratory). Currently, transmitted INSTI resistance is infrequent, but the risk of people acquiring INSTI-resistant strains may be greater in certain known exposure settings. INSTI-resistance testing should be ordered for all people with prior exposure to CAB-LA for PrEP or an INSTI-based regimen for post-exposure prophylaxis.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
For pregnant people or people who will initiate ART on the day of or soon after HIV diagnosis, treatment can be initiated prior to receiving resistance testing results.	If necessary, the ARV regimen can be modified once resistance test results are available.
If therapy is deferred, repeat genotypic resistance testing may be considered before initiation of ART **(CIII).** A genotypic assay is generally preferred **(AIII).**	Repeat testing before initiation of ART may be considered, because the person may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
In People With Virologic Failure Drug-resistance testing is recommended in people on ART with HIV RNA >200 copies/mL (**AI** for >1,000 copies/mL**, AIII** for 501–1,000 copies/mL) and a confirmed HIV RNA 201–500 copies/mL **(CIII).** In people with confirmed HIV RNA levels between 201–500 copies/mL, testing may not be successful but should still be considered.	Drug-resistance testing can help determine the role of resistance in virologic failure and maximize the ability to select active drugs for the new regimen. Resistance testing for HIV RNA levels 201–500 copies/mL may need to be conducted within a research setting.
Resistance testing should be done while the person is taking ART or, if that is not possible, within 4 weeks after discontinuation of non–long-acting ARV drugs **(AII).** If >4 weeks have elapsed, resistance testing may still be useful to guide therapy; however, previously selected mutations can be missed due to lack of drug-selective pressure **(CIII).**	The absence of detectable resistance in such people with HIV must be interpreted with caution when designing subsequent ARV regimens, as mutations may decay with time.
For people who previously received LA CAB/RPV and present with virologic failure, resistance testing (including INSTI genotypic testing) should be performed regardless of the time since the last dose of LA CAB/RPV **(AIII).**	Because of the long half-lives of LA CAB and RPV, resistance mutations to INSTI and NNRTI may emerge even months after the last doses of these drugs.
Reverse transcriptase and protease genotypic resistance testing should be performed on people with virologic failure. Integrase resistance testing should be performed on individuals who have virologic failure and have a history of prior use of an INSTI (for prevention or treatment) or are currently receiving an INSTI-based regimen **(AII).**	Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV. INSTI-resistance tests may need to be ordered separately. (Clinicians should check with the testing laboratory.)
All prior and current drug-resistance testing results should be reviewed and considered when designing a new ARV regimen for a person experiencing virologic failure **(AIII).**	Drug-resistance mutations may decay with time, and mutations detected in prior resistance tests may not be detected in current tests, though they remain clinically relevant.
Adding phenotypic testing to genotypic testing is generally preferred in people with known or suspected complex drug-resistance patterns **(BIII).**	Phenotypic testing can provide additional useful information in people with complex drug-resistance mutation patterns.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI).**	See Co-Receptor Tropism Assays section.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
In People With Suboptimal Suppression of Viral Load Drug-resistance testing is recommended in people with suboptimal viral load suppression after initiation of ART **(AII).**	Testing can determine the role of resistance in suboptimal viral suppression, and it can help the clinician identify the number of active drugs available in the current ARV regimen and assess the need for a new regimen.
In Pregnant People With HIV Genotypic resistance testing is recommended for all pregnant people before initial ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI).**	The goals of ART in pregnant people with HIV are to achieve maximal viral suppression for treatment of HIV in the pregnant person and to prevent perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal ARV regimen. However, treatment should not be delayed while awaiting resistance testing results. The initial regimen can be modified once resistance test results are available, if needed.
In People With Undetectable Viral Load or Low-Level Viremia Who Are Planning to Change Their ARV Regimen HIV-1 proviral DNA resistance assays may be useful if HIV RNA is below the limit of detection or with low-level viremia, where a HIV RNA genotypic assay is unlikely to be successful **(CIII).**	HIV-1 proviral DNA resistance assays may provide information about previously circulating resistant viral variants that are archived within proviral DNA. These assays may miss some or all prior resistance mutations that have occurred within the viral quasi-species and, therefore, they should be interpreted with caution. The clinical utility of HIV-1 proviral DNA assays has not been fully determined.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CAB-LA = long-acting cabotegravir; CCR5 = cysteine-cysteine chemokine receptor 5; INSTI = integrase strand transfer inhibitor; LA = long-acting; LA CAB/RPV = long-acting cabotegravir/rilpivirine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PrEP = pre-exposure prophylaxis; RPV = rilpivirine

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Co-Receptor Tropism Assays

Updated: October 25, 2018
Reviewed: October 25, 2018

Panel's Recommendations
• A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered **(AI).** • Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist **(BIII).** • A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage **(AI).** • A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage **(BII).** • A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification) **(BII).**
***Rating of Recommendations**: A = Strong; B = Moderate; C = Weak* ***Rating of Evidence**: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV enters cells by a complex process that involves sequential attachment to the CD4 T lymphocyte (CD4) receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes.[1] CCR5 co-receptor antagonists prevent HIV entry into target cells by binding to the CCR5 receptors.[2] Phenotypic and genotypic assays have been developed that can determine or predict the co-receptor tropism (i.e., use of CCR5, CXCR4, or both as either dual-tropic virus or a mixed population of viruses referred to for purposes of assay results as dual/mixed [D/M]) of the patient's dominant virus population. An older generation assay (Trofile,® Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in clinical trials that led to the approval of maraviroc (MVC), the only CCR5 antagonist currently available. The assay has been improved and is now available with enhanced sensitivity. In addition, genotypic assays to predict co-receptor usage are commercially available.

During acute/recent infection, the vast majority of patients harbor a CCR5-utilizing virus (R5 virus), which suggests that the R5 variant is preferentially transmitted; however, up to 19% of individuals with acute/recent infection can harbor CXCR4-tropic virus.[3-5] Viruses in many untreated patients eventually exhibit a shift in co-receptor tropism from CCR5 usage to either CXCR4 usage or D/M tropism. This shift is temporally associated with a more rapid decline in CD4 counts,[6,7] but whether this tropism shift is a cause or a consequence of progressive immunodeficiency remains undetermined.[1] Antiretroviral-treated patients with extensive drug resistance or persistently high-level viremia are more likely to harbor CXCR4- or D/M-tropic variants than untreated patients with comparable CD4 counts.[8,9] The prevalence of CXCR4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3.[8,10] Since CXCR4-tropic viruses may be present at initial presentation or a patient may shift to CXCR4-tropism over the course of infection, co-receptor tropism should always be assessed prior to the use of CCR5 antagonists for treatment. Once a patient has ever been documented with detectable CXCR4- or D/M-tropic virus, it is assumed that such viruses will always be present. CCR5 co-receptor antagonists will no longer be active for that patient and should not be used.

Phenotypic Assays

Phenotypic assays characterize the co-receptor usage of plasma-derived virus. These assays involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses, which are replication-defective, are used to infect target cell lines that express either CCR5 or CXCR4.[11,12] Using the Trofile® assay, the co-receptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors *in vitro*. This assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the Trofile® assay.[12] This earlier assay failed to routinely detect low levels of CXCR4-utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low levels of such variants at baseline, which were below the assay limit of detection, and these patients exhibited rapid virologic failure after initiation of a CCR5 antagonist.[13] The assay has been improved and is now able to detect lower levels of CXCR4-utlizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones represent 0.3% or more of the virus population.[14] Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only assay that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the Trofile® assay.

In patients with an undetectable viral load or detectable plasma HIV RNA <1,000 copies/mL, phenotypic co-receptor usage can be determined using proviral DNA obtained from peripheral blood mononuclear cells (e.g., Trofile® DNA, Monogram Sciences); however, the clinical utility of this assay remains to be determined.[15]

Genotypic Assays

Genotypic determination of HIV-1 co-receptor usage is based on sequencing of the V3-coding region of HIV-1 *env*, the principal determinant of co-receptor usage. A variety of algorithms and bioinformatics programs can be used to predict co-receptor usage from the V3 sequence.[16] When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50% to 75%) for the presence of a CXCR4-utilizing virus. Studies in which V3 genotyping was performed on samples from patients screened for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC.[17-19] An important caveat is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (Trofile®). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. Other studies have also demonstrated relatively high concordance between genotypic- and phenotypic-assessed tropism;[20,21] however, there is variability between different genotypic platforms.[22]

Given these performance characteristics, genotypic tropism assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant;[23] therefore, the Panel preferentially recommends phenotypic testing. Based on accessibility, capacity, logistics, and cost, European guidelines currently include genotypic testing as an equivalent option to phenotypic testing when determining co-receptor usage among patients with HIV RNA >1,000 copies/mL and preferentially for those with HIV RNA ≤1,000 copies/mL.[24]

HIV-1 proviral DNA genotypic tropism testing is available for patients with HIV RNA <1,000 copies/mL. These assays evaluate the HIV-1 proviral DNA integrated within infected cells for CXCR4-utilizing viral strains.[25] As discussed above, caution is advised when using such assays, as their detection limit, concordance with plasma HIV RNA tropism, and clinical utility are not yet fully determined.

Use of Assays to Determine Co-receptor Usage in Clinical Practice

An assay for HIV-1 co-receptor usage should be performed whenever the use of a CCR5 antagonist is being considered (**AI**). This is true even in the setting of prior tropism testing showing CCR5 usage, as viral evolution may occur over the course of infection. In addition, because virologic failure may occur due to a shift from CCR5-using to CXCR4-using virus, testing for co-receptor usage is recommended in patients who exhibit virologic failure on a CCR5 antagonist **(BIII).** Virologic failure may also be caused by resistance of a CCR5-using virus to a CCR5 antagonist, but such resistance is uncommon. Compared to genotypic testing, phenotypic testing has more evidence supporting its utility. Therefore, a phenotypic test for co-receptor usage is generally preferred **(AI).** However, because phenotypic testing is more expensive, requires more time to perform, and may have logistic challenges, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test **(BII).**

As with HIV resistance testing, the results of all prior tropism tests should be obtained. If CXCR4-utlizing or D/M-tropic viruses have ever been detected previously, then repeat testing is not necessary and a CCR5 co-receptor antagonist **should not be used.**

If a CCR5 co-receptor antagonist is being considered in a patient with an undetectable HIV RNA (e.g., in cases of regimen simplification or a toxicity-related switch), a proviral DNA tropism assay can be utilized **(BII).**[26-28] If CXCR4-utlizing or D/M-tropic viruses are detected, then the CCR5 co-receptor antagonist **should not be used.**

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HLA-B*5701 Screening

Updated: December 1, 2007
Reviewed: January 10, 2011

Panel's Recommendations
• The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) **(AI).** • HLA-B*5701-positive patients should not be prescribed ABC **(AI).** • The positive status should be recorded as an ABC allergy in the patient's medical record **(AII).** • When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR **(CIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion*

The abacavir (ABC) hypersensitivity reaction (HSR) is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC treatment. This reaction has been reported in 5% to 8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of ABC. Discontinuing ABC usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.[1]

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*5701.[2,3] Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR.[4] A positive ABC SPT is an ABC-specific delayed HSR that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele.[5] The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool. The PREDICT-1 study randomized participants with HIV before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC).[6] The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT and significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk of ABC HSR (100% sensitivity in black and white populations).[7]

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting an ABC-containing regimen in a person with HIV **(AI).** HLA-B*5701–positive patients should not be prescribed ABC **(AI),** and the positive status should be recorded as an ABC allergy in the patient's medical record **(AII).** HLA-B*5701 testing is needed only once in a patient's lifetime;

thus, efforts to carefully record and maintain the test result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701–positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII).**

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Treatment Goals

Updated: January 28, 2016
Reviewed: January 28, 2016

Antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality at all stages of HIV infection[1-4] and has reduced HIV transmission.[5-8] Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 T lymphocyte (CD4) cell numbers, and confers substantial clinical benefits, all of which are important treatment goals.[9, 10] HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in cohorts with HIV (see Initiating Antiretroviral Therapy). Despite these benefits, eradication of HIV infection cannot be achieved with available antiretrovirals (ARVs). Treatment interruption has been associated with rebound viremia, worsening of immune function, and increased morbidity and mortality.[11] Thus, once initiated, ART should be continued, with the following key treatment goals:

- Maximally and durably suppress plasma HIV RNA;
- Restore and preserve immunologic function;
- Reduce HIV-associated morbidity and prolong the duration and quality of survival; and
- Prevent HIV transmission.

Achieving viral suppression currently requires the use of combination ARV regimens that generally include three active drugs from two or more drug classes. Baseline patient characteristics and results from drug resistance testing should guide design of the specific regimen (see What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient). When initial HIV suppression is not achieved or not maintained, changing to a new regimen with at least two active drugs is often required (see Virologic Failure).The increasing number of ARV drugs and drug classes makes viral suppression below detection limits an achievable goal in most patients.

After initiation of effective ART, viral load reduction to below limits of assay detection usually occurs within the first 12 to 24 weeks of therapy. Predictors of virologic success include the following:

- Low baseline viremia;
- High potency of the ARV regimen;
- Tolerability of the regimen;
- Convenience of the regimen; and
- Excellent adherence to the regimen.

Strategies to Achieve Treatment Goals

Selection of Initial Combination Regimen

Several ARV regimens are recommended for use in ART-naive patients (see What to Start). Most of the recommended regimens have comparable efficacy but vary in pill burden, potential for drug interactions and/or side effects, and propensity to select for resistance mutations if ART adherence is suboptimal. Regimens should be tailored for the individual patient to enhance adherence and support long-term treatment success. Considerations when selecting an ARV regimen for an individual patient include potential side effects, patient comorbidities, possible interactions with conconcomitant medications, results of pretreatment genotypic drug-resistance testing, and regimen convenience (see Table 7).

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient-related factors, such as active substance abuse, depression, or the experience of adverse effects; and health system issues, including interruptions in patient access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART (see Adherence to Antiretroviral Therapy).

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Initiation of Antiretroviral Therapy

Updated: December 18, 2019
Reviewed: December 18, 2019

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI).** • The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV **(AII).** • When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

The primary goal of antiretroviral therapy (ART) is to prevent HIV-associated morbidity and mortality. This goal is accomplished by using effective ART to achieve and maintain a plasma HIV-1 RNA (viral load) below the quantification limits of commercially available assays. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS–defining complications, and allows persons with HIV to live a lifespan approaching that of persons without HIV.[1]

Another goal of ART is to reduce the risk of HIV transmission to sexual partners and to infants born to persons with HIV. High plasma HIV RNA levels are a major risk factor for HIV transmission; effective ART can reduce both viremia and the risk of transmission of HIV to sexual partners[2-6] and prevent perinatal transmission.[7, 8] Modelling studies and ecological studies of populations with high ART uptake and high viral suppression rates suggest that expanded use of ART may lower the incidence of HIV and, eventually, the prevalence of HIV on a community or population level.[9-11]

Two large, randomized controlled trials addressed the optimal time to initiate ART—START[12] and TEMPRANO.[13] Both studies demonstrated reductions in morbidity and mortality among individuals with HIV who had CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3 and who were randomized to receive ART immediately when compared to individuals who delayed initiation of ART.

Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining conditions and certain serious non-AIDS–defining conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, many individuals who start treatment with CD4 counts <350 cells/mm^3 do not achieve CD4 counts >500 cells/mm^3 after up to 10 years on ART,[14, 15] and they have a shorter life expectancy than those who initiated therapy at higher CD4 count thresholds.[14-16]

Fundamental to the recommendation for earlier initiation of ART in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. Unfortunately, in some individuals, the diagnosis of HIV is not made until the later stages of the disease. In a survey conducted between 2016 and 2017, it was noted that fewer than 40% of American adults had ever had an HIV test.[17] Evidence shows that many people with HIV access health care years before their HIV diagnosis but are not offered HIV testing despite recommendations from the Centers for Disease Control and Prevention (CDC) for routine testing for everyone aged 13 to 64 years.[18, 19] There are also economic benefits to early diagnosis, including prolonging life, improving the quality of life, and decreasing the costs related to the management of AIDS and its co-morbidities.[20, 21] Additionally, HIV screening is a key step in the Ending the HIV Epidemic initiative to prevent the transmission of HIV to others.[22]

Diagnosis of HIV is delayed more often in nonwhite individuals, those who inject drugs, those who live in rural communities, and older adults, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[23-25] Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current CDC recommendations is essential. The U.S. Preventative Services Task Force recommends HIV testing for persons aged 15 to 65 years and for all pregnant individuals. HIV testing should also be performed for younger and older persons when indicated. This recommendation has been designated a Grade A recommendation by the U.S. Preventative Services Task Force, meaning that third-party payers should cover this service without cost to patients.[26] It is critical that everyone who receives an HIV diagnosis be educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. In order for both individuals with HIV and their sexual partners to fully benefit from early diagnosis, clinicians should initiate ART as soon as possible and provide support to enhance retention in care and ART adherence (see Adherence to the Continuum of Care).

Initiating Antiretroviral Therapy

ART is recommended for all individuals with HIV to reduce the morbidity and mortality associated with HIV infection **(AI)** and to prevent HIV transmission to sexual partners and infants **(AI).** ART should be initiated as soon as possible after HIV diagnosis **(AII).** When initiating ART, it is important to educate patients about the goals and benefits of ART and to identify and address barriers to care engagement and treatment adherence **(AIII).** Patients should also understand that currently available ART does not cure HIV. To improve and maintain immunologic function and maintain viral suppression, ART should be continued indefinitely without interruption. Initiating ART early is particularly important for patients with AIDS-defining conditions, those with acute or recent HIV infection, and individuals who are pregnant; delaying therapy in these subpopulations has been associated with high risks of morbidity, mortality, and HIV transmission.

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

Since individuals may fail to engage in care between the initial HIV diagnosis (or first clinic visit) and the time ART is prescribed, some groups have proposed rapid ART initiation on the same day of HIV diagnosis as a strategy to increase ART uptake and engagement in care and to accelerate the time to ART-mediated viral suppression. Rapid ART initiation also has the potential to reduce the time during which people with newly diagnosed HIV can transmit HIV. The rapid ART initiation strategy is supported by randomized controlled trials that were performed in resource-limited settings outside of the United States[27-29] and observational trials in the United States that included both

immediate initiation of ART (on the day of diagnosis)[30-32] and rapid ART initiation (within days or weeks of diagnosis).[32, 33] The results from some of these studies are discussed below.

A randomized controlled trial conducted in South Africa enrolled 377 individuals who had recently received HIV diagnoses (median CD4 count was 210 cells/mm^3). Participants were randomized to receive ART on the day of diagnosis or to receive the usual care (three to five additional visits over 2–4 weeks before ART initiation). Those who received immediate ART were significantly more likely to be virally suppressed at 10 months (64% vs. 51% of patients achieved viral suppression, respectively).[27] In another randomized controlled trial conducted in Haiti, a higher proportion of participants who were randomized to receive same-day ART initiation were retained in care and had viral suppression at the end of 1 year than those who initiated ART at the standard time (3 weeks after HIV testing); survival was also higher in the same-day ART initiation group.[28] A novel randomized controlled trial in Lesotho compared same-day, home-based ART to usual care and standard clinic referral (which involved a minimum of two counseling sessions prior to ART initiation). Participants randomized to receive same-day ART initiation were significantly more likely to achieve linkage to care within 90 days after enrollment (68.6% vs. 43.1%) and virologic suppression at approximately 12 months (50.4% vs. 34.3%).[29]

There are many differences between health care in southern Africa and Haiti and in the United States—including differences in the health care systems, structural barriers to engagement in care, underlying HIV and tuberculosis (TB) epidemics, and ART regimens used—that limit the generalizability of the findings of the results from the studies described above. These studies, however, suggest that same-day initiation of ART is feasible and could potentially improve clinical outcomes.

While no randomized controlled trials have been conducted in the United States, several prospective observational studies have demonstrated the feasibility of same-day ART initiation. City-wide implementation of the San Francisco RAPID program among 225 patients who were newly diagnosed with HIV showed a median time from HIV diagnosis to ART start of 0 days (with a range of 0–56 days) and a median time from ART initiation to viral suppression (defined as <200 copies/mL) of 41 days. Over a median follow-up of 1.09 years (range 0–3.92 years), 92.1% of patients achieved virologic suppression. The RAPID study included a diverse and traditionally marginalized population, with a substantial proportion of participants having a major substance use disorder (51.4%), a major mental health disorder (48.1%), or unstable housing (30.6%).[31]

Whether rapid ART initiation improves long-term care engagement and virologic suppression is not yet known. One cohort study from France, however, found that earlier initiation of ART was negatively associated with care engagement at 1 year.[34] It should be emphasized that ART initiation on the same day of HIV diagnosis is resource intensive, and this strategy may require additional staff, multidisciplinary coordination, provision of ART starter packs, and consolidation of "usual care" patient services (e.g., clinical evaluation, education, counseling, initiation or optimization of insurance coverage, intake laboratory testing) into a 2- or 3-hour visit.[31] While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, removing structural barriers in order to facilitate rapid ART initiation may improve outcomes in the United States. The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends initiating ART at the time of diagnosis (when possible) or soon afterwards to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, and improve the rate of virologic suppression among individuals who have recently received HIV diagnoses **(AII).** This rating for this recommendation reflects the fact that only

observational trials have been conducted in the United States or other highly resourced countries, where health systems and socioeconomic contexts differ substantially from those in the countries where randomized trials were conducted.

Antiretroviral Therapy for Persons with Acute Opportunistic Infections and Malignancies

Initiation of ART in the setting of an acute, AIDS-associated opportunistic infection (OI) or malignancy can improve immune function and potentially enhance treatment success for the OI. Clinicians should refer to the Adult and Adolescent Opportunistic Infection Guidelines for a more in-depth discussion on specific OIs. Below is a list of important factors to consider when initiating ART in these situations.

- When no effective therapy exists for the OI (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy): In these situations, ART may be the only treatment that can improve immune function and clinical outcomes. ART should be initiated without delay in these patients (see the Adult and Adolescent Opportunistic Infection Guidelines for more information).
- Concerns regarding immune reconstitution inflammatory syndrome (IRIS): For some OIs, such as cryptococcal and TB meningitis, immediate ART initiation may increase the risk of serious IRIS. A short delay before initiating ART may be warranted.[35-38] After ART initation, the patient should be closely monitored for signs and symptoms associated with IRIS.
- Non-meningeal TB: In these patients, initiating ART during treatment for TB confers a significant survival advantage;[39-43] therefore, ART should be initiated as recommended in Tuberculosis/HIV Coinfection.
- For patients with mild to moderate cutaneous Kaposi sarcoma: Prompt initiation of ART alone without chemotherapy has been associated with improvement of cutaneous Kaposi sarcoma lesions, even though initial transient progression of Kaposi sarcoma lesions as a manifestation of IRIS can also occur.[44]
- For patients with malignancies that require chemotherapy:
    - A diagnosis of malignancy should not delay initiation of ART, nor should initiation of ART delay treatment for the malignancy.
    - Although an IRIS-like presentation of non-Hodgkin's lymphoma after initiation of ART has been described,[45] ART-mediated viral suppression is associated with longer survival among individuals undergoing treatment for AIDS-related lymphoma.[46]
    - Drug interactions should be considered when selecting ART, as there is the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some ritonavir-boosted or cobicistat-boosted regimens).

Evidence Supporting the Benefits of Antiretroviral Therapy in Preventing Morbidity and Mortality

Randomized Controlled Trials of Early vs. Deferred Antiretroviral Therapy

Two large randomized controlled trials, START and TEMPRANO, provide the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 count **(AI).** The results of these two studies are summarized below.

START was a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART initiation in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. The study began at a time when initiating ART was not recommended until an individual's CD4 count fell below 350 cells/mm^3. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm^3 were randomized to initiate ART at randomization (early initiation arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm^3 or until they developed a clinical indication for therapy (deferred initiation arm).

The study enrolled 4,685 participants, with a mean follow-up of 3 years. The primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events per 100 person-years) who were randomized to initiate ART early, and 96 participants (4.1%, or 1.38 events per 100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART; 95% confidence interval [CI], 0.30–0.62, $P < 0.001$). The most common clinical events reported were TB and malignancies (including both AIDS and non-AIDS malignancies). The majority of clinical events (59%) in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm^3, evidence for a benefit of initiating ART even before CD4 count declines below this threshold. Furthermore, the benefit of early ART was consistent across all participant subgroups, including gender, age, plasma HIV RNA levels, and income level of country. Although START was not sufficiently powered to compare the benefits of early ART initiation and deferred ART initiation for each category of clinical events, the benefit appeared to be particularly strong for AIDS events (HR 0.28), TB (HR 0.29), malignancies (HR 0.36), and severe bacterial infections (HR 0.39). The benefit at lower CD4 counts was primarily a reduction in the number of AIDS events, while the benefit at higher CD4 counts was primarily a reduction in the number of serious non-AIDS events. Importantly, early ART initiation also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61).[12, 47]

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm3 and who did not meet the criteria for starting ART according to World Health Organization guidelines at that time were randomized to start ART early (upon enrollment) or defer ART based on the national guidelines criteria for starting treatment. Half of the participants in each group received isoniazid for prevention of TB for 6 months and half did not. The primary study endpoint was a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases.

More than 2,000 participants enrolled in the trial, with a median follow-up of 30 months. Among the 849 participants who had baseline CD4 counts >500 cells/mm^3, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower among those who were randomized to start ART early than among those in the deferred arm, with an HR of 0.56 in favor of early ART

(95% CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART initiation is beneficial in reducing the rate of these clinical events.[13]

The TEMPRANO and START trials had very similar estimates for the protective effect of ART among individuals with HIV who had CD4 counts >500 cells/mm^3, further supporting the Panel's recommendation that ART be initiated in all patients regardless of CD4 count.

Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A randomized clinical trial[3] and several large observational cohort studies[4-6] have provided strong evidence that achieving sustained viral suppression prevents sexual transmission of HIV. Thus, a key goal of ART is to prevent transmission of HIV to seronegative sexual partners **(AI).** All persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL, including any measurable value below this threshold value, with ART prevents sexual transmission of HIV to their partners **(AII).** Patients may recognize this concept as Undetectable = Untransmittable, or U=U. The results of these studies are summarized in Antiretroviral Therapy to Prevent Sexual Transmission of HIV.

Prevention of Perinatal Transmission

The first well-established example of ART reducing the risk of HIV transmission is the use of ART during pregnancy to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing the risk of perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, the use of combination ART during pregnancy has reduced the rate of perinatal HIV transmission from approximately 20% to 30% to 0.1% to 0.5%.[7, 8] ART is thus recommended for all pregnant individuals with HIV, for both maternal health and for the prevention of HIV transmission to the newborn. In ART-naive pregnant individuals, ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy. All pregnant individuals should be tested for HIV upon confirmation of pregnancy, with testing repeated throughout pregnancy as needed for those at risk of HIV acquisition (see Maternal HIV Testing and Identification of Perinatal HIV Exposure in the Perinatal Guidelines).

Considerations When Initiating Antiretroviral Therapy

The ART regimens that are currently recommended as initial therapy in these guidelines (see What to Start) can suppress and maintain viral loads below the level of quantification in most patients who adhere to their regimens. Most of the recommended regimens have a low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

Optimizing Adherence, Antiretroviral Therapy Access, and Care Engagement

The key to successfully maintaining viral suppression is continuous access to ART and adherence to the prescribed regimen. Lack of adherence or intermittent access to ART can result in treatment failure and the emergence of drug resistance mutations that may compromise future treatment options. While optimizing adherence and linkage to care and ensuring continuous access are critical regardless of the timing of ART initiation, the evidence thus far indicates that drug resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who

initiate ART earlier.[48] It is important to discuss strategies to optimize adherence, care engagement, and ART access with all patients.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, substance use disorder, unstable housing, unfavorable social circumstances, patient concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in Adherence to the Continuum of Care. However, mental illness, substance use disorder, and psychosocial challenges are not reasons to withhold ART from a patient. Rather, these issues indicate the need for additional interventions to support adherence, and they may influence the ART regimen that is recommended (see What to Start).

Considerations for Special Populations

Elite HIV Controllers

A small subset of individuals with HIV maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as elite HIV controllers.[49, 50] There are limited data on the benefits of initiating ART in these individuals. The START and TEMPRANO studies demonstrated that initiating ART is clearly beneficial for the patient regardless of CD4 count; therefore, delaying ART to see if a patient becomes an elite controller is **strongly discouraged**. Nevertheless, significant uncertainty remains about the optimal management of elite controllers who have maintained undetectable viremia in the absence of ART for years.

Given that ongoing HIV replication occurs even in elite controllers, ART is strongly recommended for controllers with evidence of HIV disease progression, which is defined by declining CD4 counts or the development of HIV-related complications **(AIII).** Nonetheless, even elite controllers with normal CD4 counts show evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS–related diseases.[49, 51-53] One observational study suggested that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[54] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[55] Whether this potential immunologic benefit of ART in elite controllers outweighs the potential risks of ART toxicity and results in clinical benefit is unclear. Unfortunately, it is unlikely that randomized controlled trials will be able to address this question, given the very low prevalence of elite controllers. Although the START study included a number of participants with very low viral loads and demonstrated the benefit of immediate ART initiation regardless of the extent of viremia, the study did not include a sufficient number of controllers to definitively determine the clinical impact of ART in this specific population.[56] Nevertheless, there is a clear rationale for prescribing ART to elite controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.

Adolescents with HIV

Neither the START trial nor the TEMPRANO trial included adolescents. The Panel's recommendation to initiate ART in all patients is extrapolated to adolescents based on the expectation that they will derive benefits from early ART initiation that are similar to those observed in adults. Compared to adults, youth have demonstrated significantly lower levels of ART adherence and viral suppression, and higher rates of viral rebound following initial viral suppression.[57] In recent years, more adolescents have been prescribed once-daily regimens, which has increased the rate of viral suppression in this population, even though there has been no significant difference in treatment adherence.[58] Because youth often face psychosocial and other barriers to adherence, their ability to adhere to therapy should be carefully considered when making decisions about ART initiation. Although some adolescents may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to receiving care and to adherence. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support to adolescent patients (see Adolescents and Young Adults with HIV).[59]

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Antiretroviral Therapy to Prevent Sexual Transmission of HIV (Treatment as Prevention)

Updated: December 18, 2019
Reviewed: December 18, 2019

Panel's Recommendations
• All persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL, including any measurable value below this threshold value, with antiretroviral therapy (ART) prevents sexual transmission of HIV to their partners. Patients may recognize this concept as Undetectable = Untransmittable or U=U **(AII).**
• Persons with HIV who are starting ART should use another form of prevention with sexual partners (e.g., condoms, pre-exposure prophylaxis [PrEP] for the HIV-negative sexual partner, sexual abstinence) for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented **(AII).** Many experts would recommend confirming sustained suppression before assuming that there is no further risk of sexual HIV transmission **(AIII).**
• When the viral load is ≥200 copies/mL, additional methods are needed to prevent transmission of HIV to sexual partners until resuppression to <200 copies/mL has been confirmed **(AIII).**
• Persons with HIV who intend to rely upon ART for prevention need to maintain high levels of ART adherence **(AIII).** They should be informed that transmission is possible during periods of poor adherence or treatment interruption **(AIII).**
• At each visit for HIV care, clinicians should assess adherence to ART and counsel patients regarding the importance of ART to their own health as well as its role in preventing sexual HIV transmission **(AIII).**
• Providers should inform patients that maintaining a viral load of <200 copies/mL does not prevent acquisition or transmission of other sexually transmitted infections (STIs) **(AII).**
• Providers should also routinely screen all sexually active persons with HIV for STIs, both for their own health and to prevent transmission of STIs to others **(AIII).**
***Rating of Recommendations**: A = Strong; B = Moderate; C = Weak*
***Rating of Evidence**: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral therapy (ART) not only reduces morbidity and mortality for persons with HIV but has now been definitively shown to prevent sexual transmission of the virus when the plasma HIV RNA (viral load) is consistently suppressed to <200 copies/mL, which includes any measurable viral load that is lower than this threshold value. Providers who manage patients with HIV need to be aware of the data supporting treatment as prevention (TasP, which persons with HIV may recognize as Undetectable = Untransmittable or U=U), its implications, and how to operationalize this prevention strategy in clinical practice. For persons with HIV who intend to rely on TasP for HIV prevention, providers should make an individualized assessment of the person's risk tolerance, personal health, history of maintaining viral suppression on treatment, and access to health care services and ART, as well as other factors that may affect their ability to maintain a high level of adherence to ART.

Evidence That Viral Load Suppression Prevents Sexual HIV Transmission

Suppressing the HIV viral load to <200 copies/mL with ART prevents sexual transmission of HIV. Observational data collected in the early 1990s from heterosexual couples demonstrated that sexual transmission from untreated persons with HIV was rare at viral loads of <1,000 copies/mL to 1,500 copies/mL and that the risk of transmission increased in dose-response fashion with increasing viral

load.[1, 2] Additional reports[3-7] and a meta-analysis[8] supported the observation that sexual HIV transmission risk in heterosexual persons was correlated with plasma viral load, and transmission was infrequent below the lowest limits of quantification for the viral load assays used at the time.

The first prospective clinical trial designed specifically to address this question was HPTN 052, which randomized people with HIV who were in mixed HIV status couples (previously referred to as serodiscordant couples) to initiate ART early or to delay initiation. Initial results from this study were reported in 2011,[9] with final results reported in 2016.[10] The 2016 analysis reported that no phylogenetically linked sexual transmissions of HIV occurred among 1,763 couples who were followed a median of 5.5 years while the person with HIV was on ART and had a viral load <400 copies/mL for at least 6 months. Notably, four phylogenetically linked infections occurred within the 90 days after the partner with HIV had started ART and was presumably not yet virally suppressed, and four others occurred after the partner with HIV had experienced virologic failure. There were also a number of transmission events that were not phylogenetically linked, indicating acquisition from someone other than the enrolled study index partner.[11] HPTN 052 was conducted almost exclusively among heterosexual couples that lived in Africa and Asia and did not track the number or type of sexual exposures. In addition, ART was used as an adjunct to a comprehensive prevention package that provided condoms and encouraged condom use, as well as frequent testing for HIV and other sexually transmitted infections (STIs).

Three prospective observational studies—PARTNER 1,[12] PARTNER 2,[13] and Opposites Attract[14]—provided data from more diverse populations of mixed HIV status couples in which condomless sex was common. Clinical follow-up in these studies closely mimicked that of routine clinical care. Conducted in 14 European countries (PARTNER 1 and PARTNER 2) as well as Australia, Thailand, and Brazil (Opposites Attract), the investigators followed 548 heterosexual and 1,481 male-male mixed HIV status couples that engaged in 144,631 episodes of condomless vaginal or anal sex while the partner with HIV had a suppressed viral load on ART, defined as <200 copies/mL. In these studies, no phylogenetically linked transmissions were observed; however, as in HPTN 052, there were numerous non-phylogenetically linked transmissions attributed to partners outside the enrolled study couple relationship.

Integrating the Principles of Treatment as Prevention into Clinical Care

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that providers inform all persons with HIV that maintaining an HIV viral load <200 copies/mL with ART prevents sexual transmission of HIV **(AII).** This information may help motivate patients and help relieve stigma that can be a barrier to getting tested and entering into care, starting and remaining adherent to ART, and ultimately achieving and maintaining a viral load <200 copies/mL.[15] Although PARTNER 1, PARTNER 2, and Opposites Attract were designed to follow patients in the study as they would be typically be followed in clinical care for HIV, the participants reported high levels of ART adherence at study entry and many reported at least 1 year of condomless sex with an established sexual partner without transmission. As the principles of TasP are integrated into the clinical management of people with HIV who are on ART, implementation research will be critical to maximize the effectiveness of TasP in practice.

Frequency of Viral Load Assessment

The Panel has issued recommendations for viral load monitoring to manage the health of persons with HIV (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring). However, current data

are insufficient to determine whether these recommendations represent the optimal monitoring schedule for the purpose of preventing sexual transmission of HIV. In the PARTNER studies and Opposites Attract, viral loads were generally assessed every 3 to 6 months during study follow-up, usually during the course of regular HIV care. Pending further data, the Panel recommends no change to the existing recommendations for monitoring viral load (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring) **(BII).**

Time to Adequate Suppression after Starting Antiretroviral Therapy

A subgroup analysis from the Partners PrEP Study provided data regarding the risk of HIV transmission during and after the first 6 months on ART for the partner with HIV.[16] This analysis included 1,573 heterosexual East African couples in which the partners without HIV were randomized to the placebo arm of the Partners PrEP Study and were tested monthly for HIV while the viral load of the partner with HIV was assessed every 6 months. Three phylogenetically linked infections were diagnosed in the 6 months prior to the first follow-up visit for the partners with HIV. The observed incidence rate of 1.79 per 100 person-years during this initial 6-month period after the partner with HIV started ART was slightly less than the 2.08 per person-years incidence rate observed in couples in which the person with HIV was not receiving ART. Viral suppression in this study was defined as <40 copies/mL, and the three infections were diagnosed at 0 days, 56 days, and 149 days after the partner with HIV started ART. After the partners with HIV had been taking ART for ≥6 months, no further transmissions were observed.

At this time, the Panel recommends that persons with HIV who are starting ART use another form of prevention with sexual partners for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented **(AII).** Many experts would recommend confirming sustained suppression before assuming that there is no further risk of sexual transmission of HIV **(AIII).**

Adherence to Antiretroviral Therapy

Adherence to ART is paramount for persons who intend to prevent HIV transmission by achieving and maintaining a suppressed viral load. Viral rebound typically occurs within days to weeks after ART cessation and has been observed as early as 3 to 6 days after stopping treatment.[17-29] The minimum level of adherence that is required to prevent sexual transmission has not been determined and may vary depending on the ART regimen. In the key studies that defined the efficacy of TasP, adherence levels prior to study entry and during follow-up were very high. In clinical practice, most people who start ART will achieve a viral load <200 copies/mL within 6 months, but once this viral load is achieved, maintaining viral suppression can be a challenge, especially for those who have difficulty accessing ART and other HIV care. The Centers for Disease Control and Prevention (CDC) estimates that during 2015, 60% of persons with HIV and 78% of persons engaged in clinical care had viral loads <200 copies/mL at their most recent assessment.[30] Observational cohort data have demonstrated that within the first year of starting ART, up to 10% of persons with HIV can experience loss of viral suppression; however, the likelihood of maintaining a suppressed viral load generally improves over time. After a few years, 5% or fewer of persons on ART may experience loss of viral suppression.[31, 32]

The Panel recommends that persons with HIV who intend to rely upon TasP be made aware of the need for high levels of ART adherence **(AIII).** The Panel further recommends that adherence be assessed and counseling be provided at each visit for HIV care to reinforce the importance of adherence for the individual's health as well as its role in preventing HIV transmission **(AIII).**

Patients should be informed that transmission is possible during periods of poor adherence or treatment interruption **(AIII).**

Adherence can be especially challenging for certain groups of patients, such as adolescents and young adults, homeless persons, persons with active substance use disorder, and persons who are involved with the criminal justice system. Recommendations to help manage and maximize ART adherence can be found in Adherence to the Continuum of Care. Persons for whom there is concern about adherence also merit counseling on how to properly use other prevention methods, especially barrier methods that prevent STIs.

Managing Transient Viremia, or "Blips"

Highly adherent patients may experience intermittent or transient viremia, commonly termed "viral blips." Blips are defined in the context of effective treatment as a single, measurable HIV RNA level, typically <200 copies/mL, that is followed by a return to a viral load below the limit of detection or quantification. With contemporary ART regimens, about 10% of persons per year who are adherent to ART may experience a blip.[33-35] Most blips likely represent normal biological fluctuation (i.e., variation around a mean undetectable viral load) or laboratory artifact and not inadequate adherence.[36-38] Persistent viremia ≥200 copies/mL has been associated with increasing risk of virologic failure[33, 39] that, in the context of TasP, can lead to increased risk of sexual transmission.[10] The PARTNER studies and Opposites Attract excluded observation time when the viral load of the participant with HIV was ≥200 copies/mL. The frequency of blips <200 copies/mL was not reported in Opposites Attract; however, in PARTNER 1 and PARTNER 2, transient elevations in viral loads above the limit of detection (50 copies/mL in these studies) but <200 copies/ml were observed for 6% and 4% of the total follow-up time, respectively, during which time no phylogenetically linked infections were observed.

One of the clinical challenges with blips is that they can only be defined retrospectively once the viral load has returned to a suppressed value. The Panel recommends that when the viral load is ≥200 copies/mL, persons with HIV and their sexual partners should use another form of prevention (e.g., condoms, pre-exposure prophylaxis for sexual partners without HIV, sexual abstinence) to protect against HIV transmission until a viral load <200 copies/mL is achieved (AII). This recommendation applies both to persons who are starting ART (as noted earlier) and to those who have been taking ART and have achieved viral suppression but develop viral loads ≥200 copies/mL.

In cases where a patient achieves resuppression to <200 copies/mL after a detectable viral load ≥200 copies/mL, or when a patient with a viral load <200 copies/mL switches regimens (e.g., for regimen simplification or to avoid certain side effects), providers should check the viral load per recommendations in Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression, respectively **(AIII).** There are presently no data to guide how long, if at all, a person might need to continue to use another form of prevention in these two circumstances. Individualized assessment is recommended based on the length and quality of adherence and time with viral load <200 copies/mL preceding the viral load ≥200 copies/mL.

Effect of Sexually Transmitted Infections on Treatment as Prevention

The presence of STIs in a person with HIV does not appear to meaningfully alter the risk of sexual transmission when the person's viral load is <200 copies/mL. The PARTNER studies and the

Opposites Attract study regularly assessed participants for STIs, which were diagnosed in 6% of heterosexual participants and 13% to 27% of men who have sex with men. Although the authors of the studies noted that their findings could not rule out the possibility that STIs in participants with viral loads <200 copies/mL might affect the risk of HIV transmission, when viewed collectively, these data suggest that any effect is very small, since STIs were common and no linked infections were observed. The Panel recommends that patients using TasP be informed that maintaining a viral load of <200 copies/mL does not prevent acquisition or transmission of other STIs, and that it is not substitute for condoms or behavioral modifications **(AII).** Providers should also routinely screen all sexually active persons with HIV for STIs, both for their own health and to prevent transmission of STIs to others **(AIII).** Refer to CDC's Sexually Transmitted Diseases Treatment Guidelines for details.

Treatment as Prevention Applies Only to Sexual Transmission of HIV

Available clinical data only support the use of TasP to prevent sexual HIV transmission in patients with viral loads <200 copies/mL. The effectiveness of this strategy to prevent transmission from blood exposure (e.g., through nonsterile drug injection) has not been determined. In addition, while suppression of maternal viral load substantially reduces the risk of perinatal transmission and transmission through breastfeeding, it does not eliminate these risks, and transmission has occurred via breastfeeding despite continuous viral suppression (refer to the Perinatal Guidelines for details).

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What to Start: Initial Combination Antiretroviral Regimens for People With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Introduction

More than 30 antiretroviral (ARV) drugs in nine mechanistic classes are U.S. Food and Drug Administration (FDA)–approved for treatment of HIV infection. These nine classes include nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, a CD4 T lymphocyte (CD4) cell post-attachment inhibitor, a gp120 attachment inhibitor, and a capsid inhibitor. In addition, two drugs—ritonavir (RTV) and cobicistat (COBI)—are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of PIs and the INSTI elvitegravir (EVG).

Over time, incremental improvements in potency, tolerability, safety, convenience, drug interactions and genetic barriers to the emergence of drug resistance have led to streamlined recommendations for initial ARV regimens for most people with HIV. The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) now recommends initial ARV regimens based on an oral second-generation INSTI plus two NRTIs—bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC) **(AI)** or dolutegravir (DTG) plus TAF/FTC or tenofovir disoproxil fumarate (TDF)/ FTC or TDF/lamivudine (3TC) **(AI)**—for most people with HIV. In some people with HIV, the two-drug regimen DTG/3TC can be used **(AI).** When INSTI resistance is possible, such as after exposure to long-acting injectable cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) and/or if INSTI genotype results are not yet available, a boosted PI (boosted darunavir [DRV]) in combination with two NRTIs (TAF or TDF with FTC or 3TC) is recommended **(AIII).** The Panel's recommendations are summarized in Tables 6a and 6b.

Table 6a. Recommended Initial Regimens for Most People With HIV

Selection of antiretroviral therapy (ART) should be based on the regimen's virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug–drug interaction potential, cost, access, resistance test results, and the comorbid condition of the person with HIV. A pregnancy test should be performed in people of childbearing potential, and choice of ART for pregnant individuals should be guided by recommendations from the Perinatal Guidelines. Drug classes and regimens within each class are arranged first by evidence rating and, when ratings are equal, in alphabetical order. Additional initial ARV regimen options for certain clinical scenarios are listed in Table 6b below.

Table 6a. Recommended Initial Regimens for Most People With HIV Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Choice of ART during pregnancy should be guided by recommendations from the Perinatal Guidelines.
For people who do not have a history of using CAB-LA as PrEP, one of the following regimens is recommended[a]: • BIC/TAF/FTC **(AI)**

Table 6a. Recommended Initial Regimens for Most People With HIV

- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI),** except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting ART. If ART is to be started before results of genotypic testing results, the following regimen is recommended:

- DRV/c[c] or DRV/r with (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

[a] Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started pending the results of the INSTI genotype.

[b] TAF and TDF are two forms of TFV approved by the U.S. Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

[c] COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been reported during the second and third trimesters. For further information, refer to the Perinatal Guidelines.

Note: The following are available as coformulated drugs: BIC/TAF/FTC, DRV/c/TAF/FTC, DTG/3TC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ART = antiretroviral therapy; BIC = bictegravir; CAB-LA = long-acting cabotegravir; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; PrEP = pre-exposure prophylaxis; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Table 6b. Other Initial Antiretroviral Regimens for Certain Clinical Scenarios

Several antiretroviral regimens are found to be effective and tolerable as initial regimens but have some disadvantages or have fewer supporting data from randomized clinical trials compared with the recommended regimens listed in Table 6a. However, one of these regimens may be preferred for an individual with HIV in certain clinical situations (also see Table 7). These regimens are listed below.

Type of Regimen	ARV Regimen	For Certain Clinical Scenarios	Other Considerations
INSTI Plus Two NRTIs	DTG/ABC/3TC **(BI)** (if HLA-B*5701-negative)	When concern about renal- or bone-associated AEs precludes the use of TDF or TAF	Test for HLA-B*5701 before prescribing ABC; do not prescribe if HLA-B*5701-positive. Consider avoiding ABC for people with multiple CV risk factors or known CV disease.

Table 6b. Other Initial Antiretroviral Regimens for Certain Clinical Scenarios

Type of Regimen	ARV Regimen	For Certain Clinical Scenarios	Other Considerations
			Do not use in people with HBV coinfection unless an HBV-active drug, such as entecavir, TAF, or TDF is also used. Do not use following exposure to CAB-LA unless INSTI genotype shows sensitivity.
Boosted PI Plus Two NRTIs	(DRV/c[a] or DRV/r) plus (TAFor TDF[b]) plus (FTC or 3TC) **(BI)**	To avoid an INSTI-based regimen (e.g., documented INSTI resistance).	Assess for potential RTV- or COBI-related DDIs.
	(DRV/c[a] or DRV/r) plus ABC/3TC **(BII)** (if HLA-B*5701-negative)	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* When concern about renal or bone-associated AEs precludes the use of TDF or TAF	Test for HLA-B*5701 before prescribing ABC; do not prescribe if HLA-B*5701-positive. Consider avoiding ABC for people with multiple CV risk factors or known CV disease. Do not use in people with HBV coinfection unless used with an HBV-active drug other than 3TC. Assess for potential RTV- or COBI-related DDIs.
NNRTI Plus Two NRTIs	DOR/TDF/3TC[b] **(BI)** or DOR plus TAF/FTC[b] **(BIII)**	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* To avoid a PI-based regimen (e.g., with significant DDIs with concomitant medications)	
	RPV/TAF/FTC **(BII)** Only if HIV RNA <100,000 copies/mL **and** CD4 count >200 cells/mm^3	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* To avoid a PI-based regimen (e.g., with significant DDIs with concomitant medications), *and* When a single-tablet regimen containing an NNRTI and TAF is desired	Cannot take with PPI; space apart from H2 antagonist. Needs to be taken with a meal.

Table 6b. Other Initial Antiretroviral Regimens for Certain Clinical Scenarios

Type of Regimen	ARV Regimen	For Certain Clinical Scenarios	Other Considerations
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*			
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*			

[a] COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been observed during the second and third trimesters. For further information, refer to the Perinatal Guidelines.

[b] TAF and TDF are two forms of TFV approved by the U.S. Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Note: The following are available as coformulated drugs: ABC/3TC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/ABC/3TC, RPV/TAF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; CD4 = CD4 T lymphocyte; COBI = cobicistat; CV = cardiovascular; DDI = drug–drug interaction; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; H2 = histamine type 2; HBV = hepatitis B virus; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Supporting Evidence and Rationale Used for the Panel's Recommendations

The Panel's recommendations are primarily based on clinical trial data published in peer-reviewed journals and on data prepared by drug manufacturers for FDA review. In select cases, the Panel considers data from abstracts presented at major scientific meetings. The Panel considers published information from randomized prospective clinical trials with adequate sample size that demonstrate that an ARV regimen produces high rates of viral suppression, increases CD4 count, and has a favorable safety profile to be the strongest evidence on which to base recommendations. Comparative clinical trials of initial treatments generally are not designed to show significant differences in HIV-related clinical endpoints (such as progression to AIDS-defining conditions) or survival. Thus, the assessment of regimen efficacy and safety is primarily based on surrogate marker endpoints (i.e., rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include ARV drugs approved by the FDA based on bioequivalence or relative bioavailability studies that demonstrate that the exposure of the drug(s) in the new formulation or combination is comparable to the exposure of a reference drug(s) that has demonstrated safety and efficacy in randomized clinical trials. When developing recommendations, the Panel may also consider data from randomized switch studies in which a drug in an ARV initial regimen that suppressed patients' viral loads is replaced by a new drug from the same class. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they only examine the drug or regimen's ability to maintain suppression. Therefore, results from switch trials may not be directly applicable to the selection of an initial regimen and should be considered in conjunction with other data, including data from bioavailability/bioequivalence studies and from trials conducted in people taking their first ARV treatment regimen. In this section of the guidelines, the definition of an evidence rating of **II** is expanded to include supporting data from bioavailability/bioequivalence studies or randomized switch studies.

When developing recommendations, the Panel also considers tolerability and toxicity profiles, pill burden and dosing frequency, drug interaction potential, cost and access, postmarketing safety data, observational cohort data published in peer-reviewed publications, the experience of clinicians who are actively engaged in patient care, and the views of community members.

The Panel reviewed the available data to arrive at two classifications for initial ARV treatment regimens: (1) *Recommended Initial Regimens for Most People With HIV* (Table 6a) and (2) *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (Table 6b). *Recommended Initial Regimens for Most People With HIV* are those regimens with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. The Panel also recognizes that in certain clinical situations, other regimens may be preferred; these options are included in Table 6b. See Table 7 for examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous.

Many other ARV regimens are effective for initial therapy but have disadvantages when compared with the regimens listed in Tables 6a and 6b. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, and limitations for use in certain populations. These regimens are no longer included in Tables 6a and 6b. For people with HIV who have a suppressed viral load and are not experiencing any adverse effects while on a regimen that is not listed, changing to a regimen listed in Table 6a or 6b is not necessary. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.

Several tables in these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for a person with HIV. Table 7 provides information on considerations based on specific clinical scenarios and ARV drug characteristics. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 3–11, lists characteristics of individual ARV agents for initial therapy (e.g., formulations, dosing recommendations, PK, common adverse effects). Appendix B, Table 12 provides ARV dosing recommendations for people who have renal or hepatic insufficiency.

Changes Since the Last Revision of the Guidelines

Since the last revision of these guidelines, the Panel has made several important changes to the recommendations for initial therapy in people with HIV. Among these changes, the following deserve emphasis:

Changes in the Panel's Recommendations for Initial Regimens in Most People With HIV:

- The single-tablet regimen (STR) DTG/abacavir (ABC)/3TC has moved from *Recommended Initial Regimens for Most People With HIV* (Table 6a) to *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (Table 6b) due to the necessity of obtaining an HLA-B*5701 assay to avoid ABC-associated hypersensitivity, data suggesting increased risk for cardiovascular events associated with ABC, and the availability of several other options for initial therapy (see the Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy section for more information).
- Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started pending the results of the INSTI genotype test.

No Longer Recommended as Initial Antiretroviral Regimens:

- Raltegravir (RAL)-, elvitegravir/cobicistat (EVG/c)-, boosted atazanavir (ATV)-, and efavirenz (EFV)-based regimens and rilpivirine (RPV)/TDF/FTC are no longer recommended as initial therapy due to the following disadvantages compared with other regimens:
  - RAL: Low genetic barrier to resistance and higher pill burden
  - EVG/c: Drug–drug interactions with COBI and low genetic barrier to resistance of EVG
  - Boosted ATV: Toxicities, including hyperbilirubinemia, and drug–drug interactions
  - EFV: Toxicities, including neuropsychiatric effects and suicidality; low barrier to resistance; and drug–drug interactions
  - RPV/TDF/FTC: Availability of doravirine (DOR)/TDF/3TC as an STR, more drug–drug interactions than DOR, food restrictions, and HIV RNA and CD4 restrictions. RPV/TAF/3TC remains an option for those who wish to use an STR containing RPV and TAF
- The two-drug regimens darunavir/ritonavir (DRV/r) plus RAL and DRV/r plus 3TC are no longer recommended for initial therapy.
  - DRV/r plus RAL is not recommended due to the higher rate of virologic failure in people with HIV RNA >100,000 copies/mL, the low genetic barrier to resistance, and the high pill burden of RAL.[1-3]
  - DRV/r plus 3TC is not recommended because it requires a PK booster with accompanying drug interactions, and published clinical trial data are lacking.[4] For further information, see Other Antiretroviral Regimens for Initial Therapy.

Selecting an Initial Antiretroviral Regimen

The goal of ART is to improve health and prolong life for people with HIV and to prevent the transmission of HIV to others by maximizing virologic suppression. This is achieved by initiating therapy with a potent, safe, tolerable, and easy-to-adhere-to ARV regimen as soon as possible after diagnosis. Table 6a provides a list of Panel-recommended ARV regimens for most people with HIV. Some factors listed below may influence the selection of a regimen. See Table 6b and Table 7 for additional regimen recommendations to use in specific clinical scenarios.

Initial Characteristics to Consider in All People With HIV

- Pre-treatment HIV RNA level (viral load)
- Pre-treatment CD4 count
- History of prior exposure to CAB-LA or oral TDF/FTC or TAF/FTC as PrEP, or use of INSTI-based post-exposure prophylaxis (PEP)
- Suspected drug resistance (prior to availability of genotypic testing results)
- HIV genotypic drug resistance test results
  - Genotypic drug resistance testing in people without prior ARV exposure should focus on testing for mutations in the reverse transcriptase and protease genes.

  - If transmitted INSTI resistance is a concern, providers should also test for resistance mutations to this class of drugs.
- Individual preferences
- Anticipated adherence to the regimen

Presence of Specific Conditions

- Comorbid conditions: Cardiovascular disease; hyperlipidemia; renal disease; liver disease; osteopenia, osteoporosis, or other conditions associated with bone mineral density loss; psychiatric illness; neurologic disease; substance use disorder requiring narcotic replacement therapy
- Coinfections: Hepatitis B virus (HBV), hepatitis C virus, tuberculosis
- Pregnancy and potential for pregnancy: See below in General Considerations for Persons of Childbearing Potential Initiating Antiretroviral Therapy

Regimen-Specific Considerations

- Regimen's barrier to resistance
- HLA-B*5701 status (only for those considering initiation of ABC). Those who are HLA-B*5701 positive should not receive ABC. See Table 7 for regimens to initiate.
- Potential adverse effects and drug toxicities, including risk for the development of comorbid diseases
- Known or potential drug interactions with other medications (see Drug–Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of a fixed-dose combination or of STR formulations, food requirements)
- Cost and access (see Cost Considerations and Antiretroviral Therapy)

Considerations for People With Prior Use of Pre- or Post-Exposure Prophylaxis

- For people who acquired HIV after taking oral PrEP with TAF/FTC or TDF/FTC, there is concern for transmitted resistance, especially related to FTC or 3TC with the M184V/I mutation. In a cohort of people in New York City with newly diagnosed HIV, 2% had the M184V/I mutation. People who had used prior oral PrEP were four to seven times more likely to harbor resistance than people who had never used oral PrEP.[5] This reinforces the Panel's recommendation not to initiate DTG/3TC without the results of genotypic resistance testing.
- For people who acquired HIV after exposure to CAB-LA as PrEP, there is concern for INSTI resistance. CAB-LA may remain detectable after treatment discontinuation for up to 3 years in men and 4 years in women.[6] This long PK tail may contribute to the selection of drug-resistant variants in the setting of incident infection. In the HPTN 083 trial of CAB-LA as PrEP in cisgender men and transgender women, 10 of 32 people who acquired HIV after exposure to CAB-LA were found to harbor major INSTI resistance mutations.[7] This is the basis for the Panel's recommendation to obtain INSTI genotypic drug resistance testing in people with prior CAB-LA exposure and not to initiate INSTIs before these results are available and show INSTI

sensitivity. If therapy is initiated before INSTI sensitivity is confirmed, the Panel recommends initiating a boosted DRV regimen with TAF/FTC or TDF/FTC while awaiting INSTI genotype results; once INSTI sensitivity is confirmed by genotypic resistance testing, a switch to an INSTI-based regimen can occur **(AIII).**

- For people with no history of using CAB-LA for PrEP and who acquire HIV despite INSTI-based PEP use, an INSTI genotype should be obtained prior to beginning an INSTI-based regimen. However, because selection of INSTI-resistant virus is likely to be uncommon in this setting, an INSTI-based regimen could be started prior to the return of genotype results **(CIII).** This recommendation is based largely on theoretical concerns that INSTI resistance could occur in the setting of INSTI-based PEP failure, but it is likely to be uncommon. In addition, transmitted INSTI resistance remains low in the United States. For these reasons, the Panel supports using INSTI-based regimens in this setting.

General Considerations for Persons of Childbearing Potential Initiating Antiretroviral Therapy

- A pregnancy test should be performed before initiating ART.
- Clinicians should discuss intentions regarding pregnancy with all persons of childbearing potential.
- People with HIV should attain maximum viral suppression before attempting conception in order to protect their own health, prevent sexual HIV transmission to partners without HIV, and minimize the risk of perinatal HIV transmission to the infant.
- For individuals who are trying to conceive, the Panel recommends initiating a regimen designated as a *Preferred* regimen during pregnancy, as detailed in the Perinatal Guidelines.

General Considerations for INSTI-, PI-, or NNRTI-Based Regimens

Except when HIV is acquired after exposure to CAB-LA as PrEP and results from INSTI genotypic resistance testing are not available, INSTIs (specifically BIC and DTG) are recommended for initial therapy in most people because of their demonstrated efficacy, high barrier to resistance, tolerability, low potential for drug–drug interactions, convenience, and better adverse effects profile compared with NNRTIs and boosted PIs (see Tables 7 and 9).

INSTI-Based Regimens

The Panel's *Recommended Initial Regimens for Most People With HIV*, as listed in Table 6a, include one of two INSTIs: BIC coformulated with TAF/FTC **(AI);** or DTG plus TAF or TDF plus FTC or 3TC **(AI);** or coformulated DTG/3TC **(AI)** for people who have not had exposure to CAB-LA as PrEP. In those with prior exposure to CAB-LA as PrEP, these regimens should not be initiated unless a recent genotype test result showing no INSTI resistance mutations is available. If an INSTI-based regimen is initiated and viral suppression is not achieved in 8 to 12 weeks, genotypic resistance testing should be repeated, including for INSTIs.

For most people, these INSTI-containing regimens will be highly effective and have relatively infrequent treatment-limiting adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations.[8-10]

The Panel recommends a two-drug regimen of DTG/3TC for initial therapy if certain criteria are met. Data from two randomized trials showed that, in terms of virologic efficacy, DTG plus 3TC was non-inferior to a three-drug regimen of DTG plus TDF/FTC. No treatment-emergent resistance was seen in either the two-drug or the three-drug group.[11] Based on these data, DTG/3TC is not currently recommended for rapid ARV initiation as initial therapy before the availability of HBV serology, HIV RNA level, and an HIV genotypic test demonstrating sensitivity to 3TC.

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance than the first-generation INSTI-based regimens containing EVG or RAL and do not require a PK booster. Transmitted resistance to BIC or DTG is rare. Treatment-emergent resistance has been reported in individuals who failed three-drug DTG-based therapy[12-15] and BIC-based regimens.[16-19] Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens may be used in people who have not previously used CAB-LA for PrEP and plan to start ART before resistance testing results are available (e.g., with rapid initiation of ART after diagnosis). BIC-based regimens have been shown to be non-inferior to DTG-based regimens in clinical trials.[20-22]

There are data suggesting greater weight gain after initiating therapy with certain INSTI-based regimens and TAF than with other ARV drugs. The reasons for differences in weight gain are unclear and should not be a reason to withhold an INSTI- or TAF-based regimen.[23-30]

EVG- and RAL-based regimens have the disadvantage of having lower barriers to resistance than DTG- or BIC-containing regimens and therefore are no longer recommended as initial therapy. Additionally, the pill burden with RAL is higher than for other INSTI-based regimens whereas EVG-based regimens have a greater potential for drug interactions because EVG is combined with COBI, a strong cytochrome P3A4 inhibitor (see Table 7).

PI-Based Regimens

In the setting of HIV acquisition following CAB-LA exposure, an RTV- or COBI-boosted DRV regimen containing TAF or TDF plus FTC or 3TC is recommended as initial therapy if a genotypic drug resistance test indicating INSTI sensitivity is not available at the time of ART initiation **(AIII),** if resistance to INSTI is confirmed **(BI),** or in certain clinical situations, such as when INSTIs must be avoided **(BI).** DRV/c/TAF/FTC is available as an STR. Large observational cohorts found an association between some PIs, including DRV/r, and an increased risk of cardiovascular events; however, further study is needed.[31-36] COBI-boosted regimens should not be initiated during pregnancy because of inadequate drug levels. Boosted ATV is no longer recommended as initial therapy due to frequent adverse events (e.g., hyperbilirubinemia) and high rates of drug–drug interactions, including with tenofovir and acid-suppressive therapy.

Boosted ATV is no longer recommended as initial therapy due to frequent adverse events, such as hyperbilirubinemia and higher rates of drug–drug interactions (including with tenofovir and acid-suppressive therapy) compared to boosted DRV.

NNRTI-Based Regimens

NNRTI-based regimens are not recommended for initial therapy in most people with HIV, but selected regimens may be useful in some circumstances. The NNRTI-based regimens that are currently recommended by the Panel to be used in certain clinical scenarios include DOR/TDF/3TC **(BI),** DOR plus TAF/FTC **(BIII),** and RPV/TAF/FTC **(BII).** The emergence of drug resistance at the time of virologic failure has been reported with all NNRTIs, which generally have a lower barrier to resistance than INSTIs or boosted PIs.

DOR is available both as a single-drug tablet to be used with two NRTIs and as part of an STR with TDF/3TC. In randomized trials, DOR was non-inferior to both EFV and DRV/r when either of these drugs was taken in combination with two NRTIs,[37,38] but DOR has not yet been compared against INSTIs. DOR has fewer central nervous system (CNS) side effects than EFV and more favorable lipid effects than both DRV/r and EFV. DOR also has fewer potential drug interactions than EFV or RPV, and unlike RPV, the virologic efficacy of DOR is not compromised in people with high HIV RNA levels and low CD4 counts.

RPV has fewer adverse effects than EFV, and RPV/TAF/FTC is available as one of the smallest tablet sizes among STRs. However, RPV has lower virologic efficacy in people with baseline HIV RNA levels >100,000 copies/mL and CD4 counts <200 cells/mm^3 and is subject to numerous drug–drug interactions.[39] EFV is no longer recommended for initial therapy due to a relatively high rate of CNS-related side effects, reported suicidality, high rates of drug discontinuation, and numerous drug–drug interactions.

Regimens When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

In people in whom ABC, TDF, or TAF cannot be used or are not optimal, only DTG/3TC is recommended by the Panel **(AI).** Several other NRTI-sparing/limiting two-drug regimens have been evaluated in clinical trials but are not currently recommended for initial therapy due to insufficient data. For more information on these regimens, see Other Antiretroviral Regimens for Initial Therapy. Two-drug ARV options **should not be used** in pregnancy due to insufficient data, or in those with known pre-existing resistance to any of the ARVs in the combination. Tenofovir-sparing regimens **should not be used** in individuals with HBV coinfection unless a drug with HBV activity (i.e., entecavir) is also used.

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Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Updated: September 12, 2024
Reviewed: September 12, 2024

This table guides clinicians in choosing an initial antiretroviral (ARV) regimen according to various patient and regimen characteristics and specific clinical scenarios. ARV drugs/regimens that are listed in Table 6a as *Recommended Initial Regimens for Most People With HIV* and in Table 6b as *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* are included in this table (see Initial Combination Antiretroviral Regimens for People With HIV). When more than one scenario applies to a person with HIV, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. Please see Table 9 for additional information regarding the advantages and disadvantages of particular ARV medications recommended to be used as initiation therapy.

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/mm^3	**Do not use** RPV-based regimens.	Higher rates of virologic failure have been observed in those with low pre-treatment CD4 counts.
	HIV RNA >100,000 copies/mL (also see next row if HIV RNA >500,000 copies/mL)	**Do not use** RPV-based regimens.	Higher rates of virologic failure have been observed in those with high pre-treatment HIV RNA levels.
	HIV RNA >500,000 copies/mL	**Do Not Use** the Following Regimens: • RPV/TAF/FTC • DTG/3TC	For DTG/3TC, limited data are available in patients with viral loads above this threshold.
	HLA-B*5701 positive or result unknown	**Do not use** ABC-containing regimens.	ABC hypersensitivity is a potentially fatal reaction that is highly associated with the HLA-B*5701 allele.
	Prior exposure to oral TDF/(3TC or FTC) or TAF/3TC PrEP	Use DTG or BIC plus two NRTIs. DTG/3TC could be considered if testing confirms no 3TC resistance mutations.	DTG/3TC should be avoided if resistance testing results are not available, as presence of 3TC resistance mutations may lead to use of DTG monotherapy.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Prior exposure to CAB-LA for PrEP	INSTI genotype resistance testing should be performed. **If INSTI Resistance Is Present or If ART Needs to Be Started Before Genotype Test Results** • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC) **If No INSTI Resistance Is Identified** • BIC/TAF/FTC, *or* • DTG plus (TAF or TDF)[a] plus (3TC or FTC)	Mutations conferring resistance to INSTIs have been seen in association with CAB-LA PrEP. CAB-LA has a very long half-life, and drug exposure may persist at levels suboptimal to prevent infection and may select for INSTI-resistant virus.

	People with **no prior exposure** to CAB-LA for PrEP and ARV regimen should be started rapidly and before HIV drug resistance results are available.	**Avoid** ABC, DTG/3TC, and NNRTI-based regimens.
		
		Use
		• BIC/TAF/FTC, *or*
		• DTG plus (TAF or TDF)[a] plus (3TC or FTC)
		
		In People Who Used INSTI-Based ART for PEP Post-exposure Prophylaxis or Who Are Suspected to Have Acquired HIV From Someone Failing an INSTI-Based Regimen
		• Obtain INSTI genotypic resistance test and start one of the following regimens:
		  ○ BIC/TAF/FTC, *or*
		  ○ DTG plus (TAF or TDF)[a] plus (3TC or FTC)
			Transmitted mutations conferring NNRTI and NRTI resistance are more likely than mutations associated with PI or INSTI resistance.
			
			HLA-B*5701 results may not be available rapidly; thus, ABC is not recommended.
			
			Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started, pending the results of the INSTI genotype.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics	A one-pill, once-daily regimen is desired.	**STR Options as Initial ART Include the Following:** • BIC/TAF/FTC • DOR/TDF/3TC • DRV/c/TAF/FTC • DTG/ABC/3TC • DTG/3TC • RPV/TAF/FTC	**Do not use** DTG/ABC/3TC if the patient is HLA-B*5701 positive. DTG/3TC **is not recommended** if HIV RNA is >500,000 copies/mL. **Do not use** DTG/ABC/3TC or DTG/3TC in the setting of HBV coinfection without another HBV agent. **Do not use** RPV/TAF/FTC if HIV RNA is >100,000 copies/mL and CD4 count is <200 cells/mm^3.
	Food effects	**Regimens That Can Be Taken Without Regard to Food** • BIC-, DOR-, or DTG-based regimens	Oral bioavailability of these regimens is not significantly affected by food.
		Regimens That Should Be Taken With Food • DRV/r- or DRV/c-based regimens • RPV/TAF/FTC	Food improves absorption of these regimens. RPV-containing regimens should be taken with ≥390 calories of food.
Presence of Other Conditions	Chronic kidney disease (defined as CrCl <60 mL/min)	In general, **avoid TDF.** For patients with progressively declining renal function, consider avoiding all TFV-containing (TAF or TDF) regimens. Refer to Appendix B, Table 12 for specific ARV drug dosing recommendations in patients with renal impairment.	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in patients using TDF in conjunction with RTV-containing regimens. TAF has less impact on renal dysfunction than TDF. Avoid the use of TDF- or TAF-sparing regimens in the setting of HBV coinfection or unknown HBV status unless also receiving a fully active HBV regimen (see Hepatitis B Virus/HIV Coinfection).
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.	Refer to Appendix B, Table 12 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Concern for weight gain	For many people with HIV, gaining weight after starting ART is part of a "return to health." However, some ARV regimens are associated with greater weight increase than others.	Reasons for differences in weight gain among ART regimens are unknown. **Note:** Weight gain should not be a reason to avoid taking an INSTI-based regimen.
	Osteoporosis	**Avoid TDF.**[a]	TDF is associated with decreases in BMD, along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF[a] and ABC are associated with smaller declines in BMD than TDF.
	Psychiatric illnesses	**Consider avoiding** RPV-based regimens. Patients on INSTI-based regimens who have preexisting psychiatric conditions should be closely monitored. Some ARVs are contraindicated, and some psychiatric medications need dose adjustments when coadministered with certain ARVs.	RPV can exacerbate psychiatric symptoms and may be associated with suicidality. Some INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series. See the drug–drug interaction tables (Tables 24a, 24b, 24d, and 24g) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.
	Cardiac QTc interval prolongation	Consider avoiding RPV-based regimens if the patient is taking other medications with known risk of Torsades de Pointes or in patients at higher risk of Torsades de Pointes.	High RPV concentrations may cause QTc prolongation.
	High risk for CV events	Consider avoiding ABC-based regimens. Refer to Hyperlipidemia, below, for regimens associated with more favorable lipid profiles.	An increased risk of CV events with ABC has been observed in some, but not all, studies. Certain ARV regimens are associated with more favorable lipid profiles than other regimens.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Hyperlipidemia	PI/c and PI/r have been associated with hyperlipidemia. BIC, DOR, DTG, and RPV have fewer lipid effects.	TDF has been associated with lower lipid levels than ABC or TAF.
	Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care	Consider using regimens with a boosted PI or BIC or DTG.	These regimens have a high genetic barrier to resistance.
	Pregnancy	Refer to the Perinatal Guidelines for further guidance on ARV use during pregnancy.	
Presence of Coinfections	HBV infection	**Avoid regimens** that do not contain NRTIs. Use (TDF or TAF) with (FTC or 3TC) as part of the ARV regimen. **If TDF and TAF Are Contraindicated** • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ARV regimen (see Hepatitis B Virus/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV resistance mutations can emerge when these drugs are used without another drug that is active against HBV.
	HCV treatment required	Refer to recommendations in Hepatitis C Virus/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	
	Concomitant use with rifamycin antibiotics (e.g., rifabutin, rifampin, and rifapentine)	Recommended regimens may require dose adjustment. See the drug–drug interaction tables (Tables 24a, 24b, 24c, 24d, 24e, 24f, 24g, 25a, and 25b) and Tuberculosis/HIV Coinfection for information on ARV use with rifamycin antibiotics.	Rifamycin antibiotics are inducers of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, and RPV.

[a] TAF and TDF are two U.S. Food and Drug Administration–approved forms of TFV. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BMD = bone mineral density; CAB-LA = long-acting cabotegravir; CD4 = CD4 T lymphocyte; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen;

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; QTc = QT corrected for heart rate; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; UGT = uridine diphosphate glucuronosyltransferase

Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy

Updated: September 12, 2024
Reviewed: September 12, 2024

The following sections provide detailed information on antiretroviral (ARV) drugs that the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends for initial therapy for most people with HIV and for initial therapy in certain clinical scenarios (see Tables 6a and 6b in the Initial Combination Antiretroviral Regimens for People With HIV section), including ARV drug characteristics, adverse effects, clinical trial results, and Panel recommendations on their use.

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options for People Without Prior Antiretroviral Treatment

Note: Listed in order of the Panel's recommendations in Tables 6a and 6b.

Characteristics	TAF/FTC	TDF/FTC	TDF/3TC	3TC	ABC/3TC
Dosing Frequency	Once daily	Once daily	Once daily	Once daily	Once daily
Available Coformulations for People Without Prior ARV Treatment	• TAF 25 mg/FTC • BIC/TAF 25 mg/FTC • DRV/c/TAF 10 mg/FTC • RPV/TAF 25 mg/FTC	• TDF/FTC	• TDF/3TC • DOR/TDF/3TC	• DTG/3TC	• ABC/3TC • DTG/ABC/3TC
Adverse Effects	**TAF** • Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF) • Decrease in BMD (less than with TDF)	**TDF** • Renal insufficiency, proximal renal tubulopathy • Decrease in BMD • Renal and bone toxicity are exacerbated by pharmacologic boosters.	**TDF** • Renal insufficiency, proximal renal tubulopathy • Decrease in BMD • Renal and bone toxicity are exacerbated by pharmacologic boosters.	**3TC** • No notable adverse effects	**ABC** • HSR to ABC is associated with the presence of HLA-B*5701 allele.[b] • Increase in CV events is associated with ABC use in some but not all cohort studies.
Other Considerations	• Also used for HBV treatment. Discontinuation may precipitate HBV flare. • See Appendix B, Table 11 for dosing recommendations in people with renal insufficiency.			• 3TC or ABC/3TC **should not be used** as treatment for HBV without adding another HBV-active drug.	

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options for People Without Prior Antiretroviral Treatment

Characteristics	TAF/FTC	TDF/FTC	TDF/3TC	3TC	ABC/3TC
	• Some studies reported less weight gain and lower LDL, HDL, TC, and triglycerides with TDF than with TAF.				

[a] 3TC is recommended for use with DTG in some people as initial ART. See Table 6a and the discussion below for more information. Otherwise, dual-NRTI backbones are recommended.

[b] Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to patient's allergy list. See the HLA-B*5701 Screening section for more information.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BMD = bone mineral density; CV = cardiovascular; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; HDL = high-density lipoprotein; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; NRTI = nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate

Summary

The U.S. Food and Drug Administration (FDA)–approved nucleos(t)ide reverse transcriptase inhibitors (NRTIs) include zidovudine (ZDV), stavudine (d4T), didanosine (ddI), abacavir (ABC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), lamivudine (3TC), and emtricitabine (FTC). Older NRTIs (ZDV, d4T, ddI) are no longer recommended for use in clinical practice in the United States because of high rates of serious toxicities. All of these drugs can cause mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, or lipoatrophy; ZDV may cause bone marrow suppression, whereas peripheral neuropathy is commonly seen with ddI or d4T use. The incidence of these complications is substantially lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.[1,2]

TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are part of *Recommended Initial Regimens for Most People With HIV* (see Table 6a in Initial Combination Antiretroviral Regimens for People With HIV). In addition, 3TC may be used as a single NRTI with dolutegravir (DTG), except in individuals with HIV RNA >500,000 copies/mL or in whom antiretroviral therapy (ART) is to be started before the results of HIV RNA and HIV genotypic resistance tests are available. If used in those with hepatitis B virus (HBV) coinfection, another HBV-active drug should be added. Tables 6a and 6b in the Initial Combination Antiretroviral Regimens for People With HIV section provide recommendations and ratings for the individual regimens. These recommendations are based on the virologic potency and durability, short- and long-term toxicity, and dosing convenience of these drugs. TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.[3] TAF is less likely to cause kidney and bone toxicities than TDF, whereas TDF is associated with lower lipid levels than TAF. Like TDF, TAF is a recommended option in pregnancy because of reassuring data from a multinational trial in pregnant women with HIV[4] and data from the Antiretroviral Pregnancy Registry that show no evidence of teratogenicity. Please refer to the Perinatal Guidelines for more information on the use of ARVs during pregnancy.

ABC/3TC, including DTG/ABC/3TC, is no longer recommended for initial therapy in most people with HIV but may be considered in circumstances in which tenofovir (TFV)-containing regimens or DTG/3TC cannot be used. Before starting any regimen with ABC, screening for the HLA-B*5701 allele is necessary because there is a strong link with a potentially life-threatening hypersensitivity reaction in people who test positive for this allele. In addition, some data continue to support an association between ABC and an increased risk for serious cardiovascular events.[5,6]

Along with safety and efficacy, cost and access are among the factors to consider when choosing among available options. ABC/3TC, TDF/3TC, TDF/FTC, and 3TC are available as generic formulations.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

Safety and HIV Efficacy

Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of elvitegravir/cobicistat (EVG/c)/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min.

- TAF/FTC was virologically non-inferior to TDF/FTC at Week 48 (92% vs. 90% of participants had plasma HIV RNA <50 copies/mL, respectively),[7] but TAF/FTC was superior to TDF/FTC at Week 144 (84.2% vs. 80% of participants with plasma HIV RNA <50 copies/mL), largely driven by a higher rate of treatment discontinuation in the TDF arm.[8]
- Participants in the TAF arm had significantly smaller reductions in bone mineral density (BMD) at the spine and hip than those in the TDF arm through 144 weeks.[8] Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through Week 96.[9] Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at Week 96, with no change in total cholesterol to HDL ratio.[10]

Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC, with each combination administered with boosted darunavir (DRV) in ART-naive participants:

- A Phase 2 study of coformulated darunavir/cobicistat (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC in treatment-naive participants demonstrated similar virologic suppression rates in both arms (75% vs. 74%).[11] In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among participants in the TAF group.
- The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At Week 48, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.[12]

One analysis evaluated data from 14 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF and TAF when either drug was taken with or without pharmacokinetic (PK) boosters (ritonavir [RTV] or cobicistat [COBI]). No significant differences appeared between unboosted regimens with TDF and TAF in terms of virologic efficacy. When used with PK boosters, TAF resulted in a clinically small but statistically significant greater virologic efficacy than TDF (94% vs. 92%; $P = 0.0004$). No difference was seen in bone-related toxicities and clinical or laboratory adverse events between TAF and TDF, regardless of whether used with a boosting agent. The rate of discontinuation due to renal adverse events was higher for those on boosted regimens containing TDF compared with those containing TAF, with a small but statistically significant difference ($P = 0.03$).[13]

Although conducted in people without HIV for pre-exposure prophylaxis (PrEP), the DISCOVER trial, with 5,387 treated participants, was the largest trial to directly compare the adverse effects of TAF/FTC with those of TDF/FTC.[14] The following findings were observed after 48 weeks of follow-up:

- Adverse events did not significantly vary between the two groups, including Grade 3 and 4 events, serious adverse events, discontinuations due to adverse events, and overall.
- Changes in renal biomarkers and bone density significantly favored the TAF arm over TDF. One case of proximal tubular disease occurred in the TDF arm.
- LDL, HDL, and total cholesterol were significantly lower in the TDF arm than in the TAF arm, with no significant difference in the total cholesterol to HDL ratio.
- Participants in the TAF arm gained an average of 1.1 kg whereas those in the TDF arm had a mean loss of 0.1 kg.

Efficacy in People With HIV and HBV

To assess the ability of TAF to maintain HIV and HBV suppression, 72 people with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 $\log_{10}$ IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[15] In this study, 96% of participants were on a TDF/FTC-containing regimen before the switch. Key results of the study showed the following:

- Among those who switched to EVG/c/TAF/FTC, HIV suppression was maintained in 91.7% of participants at Week 48, and 91.7% of participants had HBV DNA <29 IU/mL.
- Markers of proximal tubular proteinuria and biomarkers of bone turnover decreased in those who switched to EVG/c/TAF/FTC.[15]

Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

A single-tablet regimen (STR) of DTG/3TC has now been approved as an initial ARV regimen. Please refer to the Integrase Strand Transfer Inhibitor-Based Regimens section for a full discussion.

GEMINI 1 and GEMINI 2 were identically designed randomized, double-blind clinical trials that found DTG plus 3TC non-inferior to DTG plus TDF/FTC in ART-naive adults with HIV RNA <500,000 copies/mL and eGFR ≥50 mL/min.[16,17]

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug[18-20] (see the Integrase Strand Transfer Inhibitor-Based Regimen section).[21]

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each combination was used with either efavirenz (EFV) or atazanavir/ritonavir (ATV/r). In people with baseline HIV RNA ≥100,000 copies/mL, the time to virologic failure was significantly shorter with ABC/3TC than with TDF/FTC, regardless of whether the third active drug was EFV or ATV/r. In addition, time to first adverse event was also shorter in the ABC/3TC groups.[18]

- In the HEAT study, 688 participants received ABC/3TC or TDF/FTC with once-daily lopinavir/ritonavir. Virologic efficacy was similar in the two study arms, including in a subgroup of participants with HIV RNA ≥100,000 copies/mL.[20]
- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative people with HIV who were ART-naive; all participants also received EFV. The primary study endpoint was renal safety of the regimens. Although eGFR did not differ significantly between the regimens, biomarkers associated with tubular dysfunction (retinol-binding protein and beta-2 microglobulin) increased significantly, to a greater extent in the TDF/FTC arm than the ABC/3TC arm (+50% vs. +24% and no change vs. −47%, respectively). At Week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants (59%) than among TDF/FTC-treated participants (71%).[19]

Nucleoside Reverse Transcriptase Inhibitor Options for Initial Therapy

Tenofovir Alafenamide/Emtricitabine

TAF, an oral prodrug of TFV, is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which readily converts to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. After oral administration, TAF 25 mg resulted in plasma TFV concentrations that were 90% lower than those seen with TDF 300 mg. Intracellular TFV-DP concentrations, however, were substantially higher with TAF.

Adverse Effects

Renal and Bone Effects

- In randomized controlled trials that compared TAF and TDF in people without prior ARV treatment experience or those with virologic suppression, TAF had more favorable effects on renal biomarkers and bone density than TDF.

Lipid Effects

- In randomized controlled trials in ART-naive participants, in switch studies, and in a large study of PrEP, levels of LDL and HDL cholesterol and triglycerides were lower in participants who received TDF than those who received TAF. However, total cholesterol to HDL ratios did not differ between participants receiving TAF and those receiving TDF. The clinical significance of this finding is not clear.[7,22,23]

Weight Gain

- Initiation of TAF in previously untreated individuals and in people without HIV has been associated with greater weight gain than initiation of TDF[24-26] and ABC.[25] In ADVANCE, an open-label trial conducted in South Africa that compared EFV/TDF/FTC versus DTG plus TDF/FTC versus DTG plus TAF/FTC in ART-naive participants, a greater increase in body weight was reported with initiation of TAF than with TDF.[24] This area is under intense investigation, and the reason for the difference in weight gain between regimens is still uncertain. It is also unclear whether change of ART results in reversal of weight gain.

Other Factors and Considerations

- TAF/FTC is available in fixed-dose combinations (FDCs) with bictegravir (BIC), DRV/c, EVG/c, and rilpivirine (RPV), allowing the regimens to be administered as a single pill taken once daily.
- TAF-containing regimens are approved for people with eGFR ≥30 mL/min. Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TAF, and these assessments should be repeated periodically during treatment. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in people on hemodialysis.[27] Based on the results from this study, TAF/FTC can be used without dosage adjustment in people with HIV who require hemodialysis.
- Both TAF and FTC are active against HBV. In people with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ARV regimen because these drugs have activity against both viruses (see Hepatitis B Virus/HIV Coinfection).[15]
- TAF is recommended as a preferred drug in pregnancy because of reassuring data from a multinational trial of pregnant women and data from the Antiretroviral Pregnancy Registry that show no evidence of teratogenicity.[4]

The Panel's Recommendation

- On the basis of clinical trial safety and efficacy data, and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most people with HIV when prescribed with BIC or DTG **(AI),** and as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (see Table 6b in the Initial Combination Antiretroviral Regimens in People With HIV section) when given with RPV, DOR, RTV-boosted DRV (DRV/r), or DRV/c.

Tenofovir Disoproxil Fumarate/Emtricitabine and Tenofovir Disoproxil Fumarate/Lamivudine

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted protease inhibitors (PIs), EVG/c, RAL, and DTG in randomized clinical trials.[28-37]

Adverse Effects

Renal Effects

- New onset or worsening renal impairment has been associated with TDF use.[38,39] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in women),[40] and preexisting renal impairment.[41] Adverse effects on renal biomarkers, such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.[42]
- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC than TAF/FTC with PK boosters.[13]

Bone Effects

- Although initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.[43,44] BMD generally stabilizes following an early decline after ART initiation. Loss of BMD is also greater with TDF than with TAF.
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.[45] Adverse bone outcomes have been found to be more likely when TDF/FTC is coadministered with PK boosters. However, a meta-analysis found no difference in bone-related toxicities between TAF and TDF, regardless of boosting.[13]

Other Factors and Considerations

- TDF/3TC is available as a coformulated generic drug.
- TDF/3TC is available in an FDC with DOR 100 mg.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring of People With HIV Receiving Antiretroviral Therapy). In people who have preexisting renal insufficiency (CrCl <60 mL/min),[46] use of TDF generally should be avoided. If TDF is used, a dose adjustment is required if the person's CrCl falls below 50 mL/min (see Appendix B, Table 12 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In people with HBV/HIV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ARV regimen because these drugs have activity against both viruses (see Hepatitis B Virus/HIV Coinfection).

The Panel's Recommendations

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most people with HIV when combined with DTG, and as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (Table 6b in the Initial Combination Antiretroviral Regimens for People With HIV section).
- TDF should be used with caution or avoided in people with renal disease and/or osteopenia/osteoporosis.
- When TDF is used, especially in conjunction with a PK booster, clinicians should monitor for renal and bone safety during therapy. Boosters should be avoided when possible in people taking TDF.

Emtricitabine Versus Lamivudine

FTC and 3TC generally are used interchangeably in combination with other ARVs, based on the results of randomized clinical trials and a meta-analysis of 12 trials that compared virologic efficacy and safety.[47,48] In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC

when either was combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI)—EFV or nevirapine[49]—or with a boosted PI.[50] No difference was reported in the rates of virologic failure in people who were taking TDF/FTC and people who were taking TDF/3TC when these drug combinations were used with a boosted PI. TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis; however, participants in the NNRTI cohort who were taking 3TC generally had higher viral loads and lower CD4 T lymphocyte cell counts and were more likely to be using injection drugs at the start of the study than those taking FTC.

Adverse Effects

- Both FTC and 3TC have been well tolerated with no significant treatment-limiting adverse effects.
- In early clinical trials, FTC was infrequently associated with mild hyperpigmentation of palms and soles.

Other Factors and Considerations

- 3TC is now generic in the United States and is coformulated with other drugs, such as DOR/TDF/3TC and DTG/ABC/3TC.
- Both 3TC and FTC have activity against hepatitis B but are insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of FTC or 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- See Appendix B, Table 12 for dosing recommendations in people with renal impairment.
- No significant drug interactions have been identified with FTC. Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.
- Both FTC and 3TC select for the M184V mutation when viral suppression is suboptimal.

The Panel's Recommendation

- FTC and 3TC are considered interchangeable in combination with other ARV drugs.

Lamivudine as a Single Nucleoside Reverse Transcriptase Inhibitor

Based on the GEMINI-1 and GEMINI-2 studies[17] that found DTG plus 3TC non-inferior to DTG plus TDF/FTC in ART-naive people with HIV RNA <500,000 copies/mL, 3TC may be used as a single NRTI with DTG (see Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs for more information).

Other Factors and Considerations

- 3TC with DTG is available as a STR.
- 3TC is active against HBV but is insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- 3TC is available in two brand-name formulations (one for HIV and the other for HBV), but the doses are different. The dose for HIV treatment is 3TC 300 mg daily.

- See Appendix B, Table 12 for dosing recommendations in people with renal impairment.
- Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.

The Panel's Recommendations

The Panel recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People With HIV,* with four exceptions. DTG/3TC **is not recommended** for:

- Individuals with HIV RNA >500,000 copies/mL.
- Individuals with HBV coinfection unless receiving another HBV-active drug.
- Individuals who have received long-acting injectable cabotegravir as PrEP and do not have integrase strand transfer inhibitor (INSTI) genotype resistance testing results available demonstrating INSTI sensitivity.
- Individuals starting ART before the results of genotypic resistance testing for reverse transcriptase are available.

Abacavir/Lamivudine

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in people who are ART-naive.[21,51-53]

Adverse Effects

Hypersensitivity Reactions

- Clinically suspected hypersensitivity reactions (HSRs) were observed in 5% to 8% of individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele; approximately 50% of people who are HLA-B*5701-positive and are given ABC will have a related HSR.[54,55] HLA-B*5701 testing should be done if the use of ABC is being considered. A person who tests positive for HLA-B*5701 should not be given ABC, and ABC hypersensitivity should be noted on the person's allergy list. People who are HLA-B*5701 negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. People who discontinue ABC because of a suspected HSR **should never be rechallenged,** regardless of their HLA-B*5701 status.

Cardiovascular Risk

- An association between ABC use and myocardial infarction (MI) was first reported in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. This large, multinational, observational study group found that recent (i.e., within 6 months) or current use of ABC was associated with an increased risk of an MI, particularly in participants with preexisting cardiac risk factors.[5,6]
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.[56-63] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[64-68]

- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

Other Factors and Considerations

- ABC/3TC is available as a coformulated tablet and as a coformulated STR with DTG.
- ABC and 3TC are available separately and as a coformulated tablet in generic tablet formulations.
- ABC does not cause renal dysfunction and can be used instead of TDF in people with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in people with renal dysfunction.

The Panel's Recommendations

- ABC should be prescribed only for people who are HLA-B*5701 negative.
- Due to the need for HLA-B*5701 testing before use, ongoing concerns about increased risk of cardiovascular events seen in association with ABC (observed in some but not all studies), and the availability of other effective and well-tolerated options, the Panel no longer recommends DTG/ABC/3TC for most individuals initiating ART and now classifies DTG/ABC/3TC as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (see Table 6b in the Initial Combination Antiretroviral Regimens in People With HIV section) **(BI)** (see Characteristics of Integrase Strand Transfer Inhibitors for discussion regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with DRV/r or DRV/c is also recommended as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (Table 6b in the Initial Combination Antiretroviral Regimens in People With HIV section) **(BII).**
- ABC should be used with caution or avoided in people with cardiovascular disease or known high cardiovascular risk.

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Integrase Strand Transfer Inhibitor–Based Regimens as Initial Antiretroviral Therapy

Updated: September 12, 2024
Reviewed: September 12, 2024

Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended as Part of Initial Antiretroviral Therapy

	BIC	DTG
Dosing Frequency	Once daily	**Once Daily** • As initial ART or in people with no INSTI-resistance mutations **Twice Daily** • If used with certain CYP3A4 and UGT1A1 inducers; *or* • In people with certain INSTI drug resistance mutations
STR Available as Initial ART	BIC/TAF/FTC	• DTG/ABC/3TC • DTG/3TC
Available as a Single Drug Tablet	No	Yes
Virologic Efficacy Against EVG- or RAL-Resistant HIV	*In vitro* data indicate activity, but clinical trial data are not available.	Yes, for some isolates; effective with DTG 50 mg twice-daily dose
Adverse Reactions	• ↑ CPK 4% • CNS side effects were rarely reported in clinical trials. • Diarrhea, nausea, and headache may occur in some cases.	• ↑ CPK, myositis • CNS side effects such as insomnia and headache have been reported; depression and suicidality are rare, occurring primarily in people with preexisting conditions. • Hypersensitivity, hepatotoxicity
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate (minor)
Chelation With Polyvalent Cation Supplements and Antacids	Oral absorption may be reduced by polyvalent cations. See Table 24d for recommendations regarding dosing separations and these drugs.	
Other Key Potential Drug Interaction Mechanisms	P-gp substrate, UGT1A1 substrate, OCT2 and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate
Other Factors	Both BIC and DTG decrease tubular secretion of creatinine without affecting glomerular function. This may result in an increase in serum creatinine of approximately 0.1–0.2 mg/dL.	

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; CNS = central nervous system; CPK = creatine phosphokinase; CYP = cytochrome P450; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MATE1 = multidrug and toxic compound extrusion 1; OCT2 = organic cation transporter 2; P-gp = p-glycoprotein; RAL = raltegravir; STR = single-tablet regimen; TAF = tenofovir alafenamide; UGT = uridine diphosphate glucuronosyltransferase

Four oral integrase strand transfer inhibitors (INSTIs)—bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL)—are approved for use in people with HIV as their initial ARV treatment. Intramuscular cabotegravir (CAB) is approved for use with rilpivirine (RPV) (with or without an oral CAB + RPV lead-in) as part of a long-acting injectable complete antiretroviral (ARV) regimen to replace a stable oral regimen in people with HIV and viral suppression. The role of this combination is discussed in the Optimizing Antiretroviral Therapy in the Setting of Viral Suppression section. Long-acting injectable cabotegravir (CAB-LA) is also approved for pre-exposure prophylaxis (PrEP). The first-generation INSTIs EVG and RAL have some disadvantages, which include a low barrier to resistance. In addition, because EVG has to be given with cobicistat (COBI), a pharmacokinetic (PK) booster, it has a high potential for drug–drug interactions, whereas RAL-based regimens have a higher pill burden than other INSTI regimens. Because of these disadvantages, elvitegravir/cobicistat (EVG/c) and RAL are no longer recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) as initial ART. Because the second-generation INSTIs BIC and DTG have high barriers to resistance, BIC/tenofovir alafenamide (TAF)/emtricitabine (FTC) and DTG plus TAF/FTC or tenofovir disoproxil fumarate (TDF)/FTC are recommended for most people with HIV (see Appendix B, Table 6 for more information on the INSTIs BIC and DTG).

This section of the guidelines will focus on BIC and DTG, the two INSTIs recommended by the Panel as part of the *Recommended Initial Regimens for Most People With HIV* (Table 6a) and *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (Table 6b) (see Tables 6a and 6b and Table 7).

Panel's Recommendations for Integrase Strand Transfer Inhibitor–Based Regimens as Initial Therapy

The Panel recommends one of the following INSTI-based regimens as initial ART for people with HIV who do not have a history of using CAB-LA as PrEP (see Table 6a in Initial Combination Antiretroviral Regimens for People With HIV):

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF) with (FTC or lamivudine [3TC]) **(AI)**
- DTG/3TC **(AI),** except for those with HIV RNA >500,000 copies/mL, with hepatitis B virus (HBV) coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

INSTI resistance has been reported in people who acquired HIV following exposure to CAB-LA as PrEP.[1] For a person who has had exposure to CAB-LA as PrEP, an INSTI-containing regimen should not be initiated unless an INSTI genotypic resistance test result is available and shows no INSTI-resistance mutations **(AIII).** If treatment is initiated before genotypic test results are available, boosted darunavir (DRV) plus (TAF or TDF) plus (FTC or 3TC) should be used, pending INSTI resistance results **(AIII).** See Table 6a in Initial Combination Antiretroviral Regimens for People With HIV for more details.

Because of the low rates of transmitted INSTI resistance in the United States at present, when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started pending the results of the INSTI genotype test.

For people who have never used CAB-LA for PrEP and who acquired HIV despite using INSTI-based post-exposure prophylaxis, an INSTI genotype should be obtained prior to beginning an INSTI-based regimen. However, because selection of INSTI-resistant virus is likely to be uncommon in this setting, an INSTI-based regimen could be started prior to the return of genotype results **(CIII).**

The Panel also recommends using DTG/abacavir (ABC)/3TC **(BI)** when concerns about renal or bone-associated adverse events preclude the use of TAF or TDF. However, ABC should only be given to people who are documented to be HLA-B*5701-negative.

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Adverse Effects

BIC and DTG are generally well tolerated, although there are reports of insomnia in some people. Depression and suicidal ideation, primarily in people with a history of psychiatric illnesses, have been reported rarely in those receiving INSTI-based regimens.[2-5]

Among people with HIV who have not yet received ART, initiation of INSTI-containing regimens has been associated with greater weight increases compared to non-nucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI) regimens.[6-11] In randomized trials of ARV-naive individuals, the mean increase in weight from baseline associated with BIC and DTG was similar and greater than with EVG/c or with efavirenz (EFV).[8,12-14] Weight gain was also greater in those initiating TAF than other nucleoside reverse transcriptase inhibitors (NRTIs).[7,8,15] These weight increases appear to disproportionately affect women and Black and Hispanic people,[6-8,16] yet predictors and mechanisms for the weight gain are still unclear. In general, concerns for weight gain should not be a reason to avoid an INSTI- or TAF-based regimen.

Integrase Strand Transfer Inhibitor Use in People of Childbearing Potential

Clinicians should refer to the Perinatal Guidelines for detailed recommendations on ARV regimens in treatment-naive people, including recommendations on the use of INSTI-based regimens during conception and throughout pregnancy.

- Earlier data from a birth outcomes surveillance study in Botswana raised concern about an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[17,18] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[19] Based on these data, DTG is now the preferred INSTI for pregnant individuals with HIV. See the Perinatal Guidelines for further discussion.
- BIC is recommended as an alternative INSTI during pregnancy because data about safety, PK, and efficacy in pregnancy are available but are more limited than data about drugs classified as *Preferred* by the Perinatal Guidelines. See the Perinatal Guidelines for more details.

Bictegravir

BIC is approved by the U.S. Food and Drug Administration for initial therapy in adults with HIV as a component of a once-daily single-tablet regimen with TAF and FTC.

Efficacy in Clinical Trials

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3 randomized double-blind clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at Week 48.
  - The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At Week 96, 84% of participants in the BIC arm and 86% of those in the DTG arm achieved HIV RNA <50 copies/mL.[15]
  - The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At Week 96, 88% of participants in the BIC/TAF/FTC arm and 90% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL.[20]
  - Week 144 follow-up from both trials demonstrated noninferiority of the BIC/TAF/FTC regimen to both DTG-containing regimens, with high levels of virologic suppression and no treatment-emergent resistance.

Adverse Effects

- BIC is generally well tolerated.
- Neuropsychiatric adverse events have been reported with INSTIs. BIC-associated serious neuropsychiatric effects were uncommon (<1%) in clinical trials and mainly occurred in the setting of preexisting depression, other psychiatric illness, or prior suicide attempt.[21]

Drug–Drug Interactions

Note: See Table 24d for a comprehensive list of potential INSTI-related drug–drug interactions.

- BIC is a cytochrome P450 (CYP) 3A4 substrate and a uridine diphosphate glucuronosyltransferase (UGT) 1A1 substrate; therefore, its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in loss of therapeutic effect of the ART. For people who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anti-seizure medications and St. John's wort should also be avoided.[21]
- BIC is an inhibitor of the drug transporters OCT2 (organic cation transporter 2) and MATE1 (multidrug and toxic compound extrusion 1); therefore, BIC may increase concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.

- Like other INSTIs, oral absorption of BIC may be reduced when BIC is coadministered with polyvalent cations (e.g., aluminum-, magnesium-, or calcium-containing antacids; calcium or iron supplements).

Other Factors and Considerations

- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are observed typically within the first 4 weeks of BIC therapy (with a median increase of 0.10 mg/dL after 48 weeks). This increase is comparable to that seen with other ARV drugs that have a similar effect on creatinine secretion, including DTG, RPV, and COBI.
- Treatment-emergent mutations that confer BIC resistance have rarely been reported in people receiving BIC for initial therapy.[22] BIC has not been studied in prospective trials for people with prior INSTI failure or INSTI-related resistance mutations. One analysis of 20 individuals with preexisting INSTI-related resistance mutations showed maintenance of virologic suppression in 19 people after switch to BIC, and viral suppression after beginning BIC in one person without prior ARV treatment. There are, however, insufficient data at present to recommend BIC use in such cases.

The Panel's Recommendation

The Panel recommends the use of BIC/TAF/FTC as a *Recommended Initial Regimen for Most People With HIV* **(AI)** (see Table 6a and Table 7 for more detailed recommendations).

Dolutegravir

As initial ARV regimens, both DTG plus two NRTIs and DTG/3TC demonstrated high efficacy in achieving HIV suppression in clinical trials. DTG is given once daily, with or without food.

Efficacy in Clinical Trials

The efficacy of DTG in ART-naive individuals has been evaluated in several fully powered randomized controlled clinical trials. In these trials, DTG-based regimens were noninferior or superior to a comparator INSTI-, NNRTI-, or PI-based regimen. The primary efficacy endpoint in these clinical trials was the proportion of participants with plasma HIV RNA <50 copies/mL.[13,23,24]

DTG Plus Two NRTIs Versus Other INSTIs Plus Two NRTIs

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared to BIC/TAF/FTC in two randomized controlled trials. These regimens have virologic efficacy that is similar to BIC/TAF/FTC (see discussion in the BIC section above).[15,20,23,25]

DTG Plus Two NRTIs Versus EFV Plus Two NRTIs

- The SINGLE trial compared DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At Week 48, DTG plus ABC/3TC was superior to EFV/TDF/FTC, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.[26] At Week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[27]
- The ADVANCE trial, an open-label, noninferiority trial conducted in South Africa, compared DTG with either TDF/FTC or TAF/FTC to EFV/TDF/FTC. At Week 96, the DTG-based

regimens were noninferior to the EFV regimen based on the proportion of participants with HIV RNA levels <50 copies/mL (79% in DTG/TAF/FTC vs. 78% in DTG/TDF/FTC vs. 74% in EFV/TDF/FTC arms). More participants discontinued the trial regimen in the EFV group than in the DTG group. Mean weight gain was 7.1 kg in the DTG/TAF/FTC group, 4.3 kg in the DTG/TDF/FTC group, and 2.3 kg in the EFV/TDF/FTC group and was greater among women than men.[14]

DTG Plus Two NRTIs Versus Ritonavir-Boosted Darunavir Plus Two NRTIs

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to the boosted PI—darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily—each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At Week 48, DTG was superior to DRV/r, with 90% and 83% of participants achieving HIV RNA <50 copies/mL, respectively. More participants discontinued their assigned regimen in the DRV/r arm.[28] The difference in efficacy between the DTG and DRV/r regimens was more pronounced in people with pre-treatment HIV RNA levels >100,000 copies/mL. At Week 96, DTG remained superior to DRV/r.[29]

DTG/3TC

- In the GEMINI-1 and GEMINI-2 trials, 1,433 ART-naive participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive DTG plus 3TC or DTG plus TDF/FTC. At Week 96, DTG plus 3TC was noninferior to DTG plus TDF/FTC with 86% of participants in the DTG plus 3TC group and 89.5% in the DTG plus TDF/FTC group with viral load <50 copies/mL.[30] Virologic nonresponse was uncommon, occurring in 3.1% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No treatment-emergent NRTI or INSTI resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the rate of HIV RNA <50 copies/mL at Week 96 was lower in the DTG plus 3TC group than in the DTG plus TDF/FTC group; however, the difference was not related to a higher rate of virologic failure in the two-drug group. Overall mean change in weight from baseline was 3.1 kg in the DTG plus 3TC group and 2.1 kg in the DTG plus TDF/FTC group. At Week 144, DTG plus 3TC maintained noninferiority to DTG plus TDF/FTC with 82% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with viral load ≥50 copies/mL was 3% in both treatment groups. A lower risk of drug-related adverse events was found with DTG plus 3TC versus DTG plus TDF/FTC (20% vs. 27%; relative risk, 0.76 [95% confidence interval, 0.63–0.92]).[30]
- Two other small, nonrandomized single-arm studies showed similar rates of viral suppression with DTG plus 3TC.[31,32]

Adverse Effects

- DTG is generally well tolerated. The most reported adverse reactions of moderate-to-severe intensity were insomnia and headache.
- Some studies have shown greater weight increase among people initiating INSTI-based regimens, including regimens with DTG.[7,8,33,34] In a pooled analysis of eight randomized controlled trials in ART-naive individuals, the weight gain at 96 weeks with BIC- and

DTG-based regimens was similar (approximately 3.5 kg). The clinical significance of weight gain in this setting is unclear.[8]

- Neuropsychiatric adverse events (e.g., sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and other INSTIs have been reported.[2,3,35,36] However, analyses of data from large randomized controlled trials and a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and regimens that included RAL, EFV, DRV, and ATV.[37] Neuropsychiatric events rarely led to DTG discontinuation.

Drug–Drug Interactions

Note: See Table 24d for a comprehensive list of potential INSTI-related drug–drug interactions.

- DTG has fewer drug interactions than BIC.
- DTG oral absorption may be reduced when the ARV is coadministered with polyvalent cations. DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives are taken. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.

Other Factors and Considerations

- DTG decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment.
- Treatment-emergent mutations that confer DTG resistance have been rarely reported in people receiving DTG as part of a three-drug regimen for initial therapy.[38-40] The incidence of resistance with DTG is much lower than with EVG or RAL, which suggests that DTG, like BIC, has a higher barrier to resistance than EVG or RAL.

The Panel's Recommendations

- The Panel classifies the following as *Recommended Initial Regimens for Most People With HIV* (see Table 6a and Table 7 for more detailed recommendations):
  - DTG plus (TAF or TDF) plus (FTC or 3TC) **(AI)**
  - DTG/3TC **(AI)—not recommended** for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
- The Panel recommends DTG/ABC/3TC **(BI)** in certain clinical scenarios for people with HIV who are documented to be HLA-B*5701-negative and who have concerns about renal or bone toxicities associated with TAF or TDF. This regimen should not be used in people with HBV coinfection unless an HBV-active drug (i.e., entecavir) other than 3TC is used.

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Non-Nucleoside Reverse Transcriptase Inhibitor–Based Regimens as Initial Antiretroviral Therapy

Updated: September 12, 2024
Reviewed: September 12, 2024

Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors That Are Recommended as Initial Antiretroviral Therapy in Certain Clinical Scenarios

Characteristics	DOR	RPV[a]
Dosing Frequency	Once daily	Once daily
Food Requirement	With or without food	With a meal
STR Available as Initial ART Recommended in Table 6b	DOR/TDF/3TC	RPV/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	Generally well tolerated	• Depression • Headache • Skin rash • QTc prolongation
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate
Other Significant Drug Interactions	None	RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is not recommended; see Drug–Drug Interactions for dosing recommendations when RPV is coadministered with an H2 blocker or antacids.

[a] See Optimizing Antiretroviral Therapy section and Appendix B, Table 4 for information regarding injectable RPV.

Key: 3TC = lamivudine; ART = antiretroviral therapy; CYP = cytochrome P; DOR = doravirine; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

Four non-nucleoside reverse transcriptase inhibitors (NNRTIs)—doravirine (DOR), efavirenz (EFV), nevirapine (NVP), and rilpivirine (RPV)—are currently approved by the U.S. Food and Drug Administration (FDA) for the initial treatment of HIV when used in combination with other antiretroviral (ARV) drugs. A fifth NNRTI, etravirine (ETR), is approved only for people who are ART-experienced.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs (especially EFV and RPV) include the prevalence of NNRTI-resistant viral strains in people without prior antiretroviral therapy (ART),[1] a low barrier for

the development of resistance, and potential for drug–drug interactions, although drug–drug interactions are less common with DOR. Resistance testing should be performed before initiation of an NNRTI-based regimen in people without prior ART. High-level resistance to all NNRTIs (except ETR or DOR) may occur with a single mutation. In people treated with RPV, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.[2,3] DOR-based regimens and one of the RPV-based regimens are now categorized as recommended *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios*. More details about these NNRTIs are provided below.

This section of the guidelines focuses on DOR and RPV, the two NNRTIs recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) as part of an initial ART regimen for people with HIV in certain clinical scenarios (see Table 6b in the Initial Combination Antiretroviral Regimens for People With HIV section and Table 7). There is no clinical trial comparing the efficacy of these two NNRTIs as initial ARV regimens. The Panel no longer recommends EFV as initial therapy because of the high incidence of serious toxicities, including neuropsychiatric effects and suicidality. NVP is no longer commonly used in clinical practice in the United States due to a relatively high potential for adverse effects compared to other NNRTIs.

Doravirine

Efficacy in Clinical Trials

The efficacy of DOR-based therapy as initial ART was demonstrated in two randomized, double-blind, placebo-controlled trials.

Doravirine-Based Regimen Versus Efavirenz-Based Regimen

- In the DRIVE-AHEAD trial, 734 participants received either DOR/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or EFV/TDF/emtricitabine (FTC), both as a daily fixed-dose combination (FDC) tablet.[4]
    - At 96 weeks, DOR/TDF/3TC was noninferior to EFV/TDF/FTC, with 77.5% of participants who received DOR/TDF/3TC and 73.6% of those who received EFV/TDF/FTC achieving HIV RNA <50 copies/mL. Although virologic responses to ART overall were lower in participants with pre-treatment HIV RNA >100,000 copies/mL or pre-treatment CD4 T lymphocyte (CD4) cell counts of ≤200 cells/mm^3, there was no difference between the DOR-treated and EFV-treated participants.
    - Virologic rebound and virologic nonresponse were similar in the DOR/TDF/3TC (9.3%) and EFV/TDF/FTC (7.7%) treatment groups. At 96 weeks, genotype resistance results were reported for 21 participants with protocol-defined virologic failure in the DOR arm and 15 participants in the EFV arm. For the DOR arm, 7 of 21 (33.3%) participants had NNRTI resistance and 6 of 21 (28.6%) had NRTI resistance. For EFV, 10 of 15 (66.7%) participants had NNRTI resistance and 5 of 15 (33.3%) had NRTI resistance.
    - More participants in the EFV arm discontinued their assigned ART due to adverse events than in the DOR arm (6.6% vs. 3.0%). Neuropsychiatric side effects and rash were more common in the EFV arm.

Doravirine-Based Regimen Versus Darunavir/Ritonavir-Based Regimen

- In the DRIVE-FORWARD trial, 769 participants received DOR or darunavir/ritonavir (DRV/r) once daily along with two investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs), either abacavir (ABC)/3TC or TDF/FTC.[5]
  - At 48 weeks, DOR was noninferior to DRV/r with 84% of study participants who received DOR versus 80% of those who received DRV/r achieving HIV RNA <50 copies/mL. Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.
  - At 96 weeks, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).[5]
  - Protocol-defined virologic failure was similar in the DOR and DRV/r groups (9% vs. 11%) by Week 96. Genotype resistance results were reported for 11 and 14 participants with virologic failure in the DOR and DRV/r arms, respectively. Treatment-emergent resistance to any study drug occurred in 2 of 11 participants in the DOR group and 1 of 14 participants in the DRV/r group.
  - Treatment-related diarrhea was more frequently reported in the DRV/r arm. Greater increases in fasting low-density lipoprotein cholesterol, triglycerides, non–high-density lipoprotein cholesterol, and total cholesterol were seen in the participants who received DRV/r than in those who received DOR.
- In a pooled analysis of DRIVE-AHEAD and DRIVE-FORWARD participants who entered an open-label extension phase following the initial 96 weeks of randomized treatment, 550 participants continued their DOR-based regimen and 502 participants switched to a DOR-based regimen from the control arms. At 192 weeks, 83% percent of participants who continued on DOR and 81% of participants in the switch arm maintained viral suppression. Discontinuation due to drug-related adverse events was <1% overall and similar between the two arms, with no discontinuations due to renal adverse events.[6]

Other Factors and Considerations

- DOR is available as a single-drug 100-mg tablet[7] and as part of a single-tablet regimen (STR) that contains DOR/TDF/3TC 100 mg/300 mg/300 mg[8] and is dosed once daily, with or without food.
- DOR-based regimens have not been directly compared to integrase strand transfer inhibitor (INSTI)–based regimens in clinical trials and have not been studied with tenofovir alafenamide (TAF) in clinical trials.
- A post hoc analysis of three randomized controlled trials examined weight gain among ART-naive participants receiving DOR versus DRV/r or EFV. At week 96, mean weight gain was similar in the DOR group (2.4 kg), DRV/r group (1.8 kg), and EFV group (1.6 kg). No significant differences between treatment groups were found in the proportion of participants whose body mass index classification increased to overweight or obese at Week 48 or Week 96.[9]
- DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see Table 24b). DOR is not a CYP3A4 inducer or inhibitor; thus, it is not expected to affect the concentrations of concomitant CYP3A4 substrates.

- Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.[10]
- There are currently no data on the safety of DOR use during pregnancy.
- There are limited clinical trial data with the combination of DOR + ABC/3TC, so the Panel is less certain about the efficacy of this regimen.

The Panel's Recommendations

- Based on the clinical trial data discussed above, the Panel classifies DOR/TDF/3TC **(BI)** and DOR plus two NRTIs (**BI** for TDF/FTC and **BIII** for TAF/FTC) as *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios*.

Rilpivirine

Oral RPV is approved for use in combination with two NRTIs as initial ART for people with HIV who have pre-treatment viral loads <100,000 copies/mL. RPV is also approved as an extended-release injectable suspension as part of a long-acting (LA) injectable complete ARV regimen when used with cabotegravir (CAB), an INSTI. This regimen is approved to replace oral ART in people with virologic suppression and no history of resistance to RPV or INSTIs (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for discussion of LA CAB/RPV).

Efficacy in Clinical Trials

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.[11] At 96 weeks, the following findings were reported:
  - RPV was noninferior to EFV overall.
  - Among participants with pre-ART viral loads >100,000 copies/mL, more RPV-treated participants experienced virologic failure than EFV-treated participants. NNRTI and NRTI resistance were more frequently found in RPV-treated participants with virologic failure.
  - Among the RPV-treated participants, the rate of virologic failure was greater in those with pre-treatment CD4 counts <200 cells/mm^3 than in those with CD4 counts ≥200 cells/mm^3.
- STaR, a Phase 3b, open-label study, compared two STRs—RPV/TDF/FTC and EFV/TDF/FTC—as initial ART in 786 people with HIV. The results at 96 weeks[12] were similar to those reported at 48 weeks.[13]
  - RPV was noninferior to EFV overall.
  - RPV was superior to EFV in participants with pre-ART viral loads ≤100,000 copies/mL and noninferior in those with pre-ART viral loads >100,000 copies/mL. Among participants with pre-ART viral loads >500,000 copies/mL, virologic failure was more common in RPV-treated than in EFV-treated participants.
  - At Week 96, there were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (5.3% vs. 1.0%, respectively).
- The STR of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence study. In this study, plasma concentrations of RPV, FTC, and TAF 25 mg in participants taking

the coformulated drug were similar to those seen in participants who received RPV as the single-drug tablet and TAF/FTC as part of the STR of EVG/c/TAF 10 mg/FTC.[14]

Adverse Effects

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of CNS adverse events (e.g., abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than in the EFV arms, and fewer people in the RPV arms discontinued therapy due to adverse events. However, up to 9% of clinical trial participants experienced depressive disorders, including approximately 1% of participants who had suicidal thoughts or who attempted suicide. People receiving RPV who have severe depressive symptoms should be evaluated to assess whether the symptoms may be due to RPV and if the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations

- Oral RPV is formulated both as a single-drug tablet and in STRs with TAF/FTC, with TDF/FTC, and with DTG. Among available STRs, RPV/TDF/FTC is no longer recommended by the Panel for initial therapy.
- RPV is also available as part of an LA injectable ARV regimen for use in combination with LA CAB in people with HIV who are virologically suppressed and do not have resistance to these drugs (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- The STR of RPV/TAF/FTC is given once daily and must be administered with a meal (containing at least 390 kcal).
- RPV is also coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for people with HIV who have achieved viral suppression.[15] However, this combination has not been studied in people with HIV and no prior ART, and it **is not recommended** for initial therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- The oral drug absorption of RPV can be significantly reduced in the presence of acid-reducing agents. RPV is **contraindicated** in people who are receiving proton pump inhibitors and should be used with caution in those receiving H2 antagonists or antacids (see Drug–Drug Interactions for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug–Drug Interactions).
- At doses above the approved dose of 25 mg, RPV may cause QTc interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

The Panel's Recommendations

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, substantial drug–drug interactions, and a low genetic barrier to resistance, RPV is **not recommended** for initial therapy in most persons with HIV. RPV/TDF/FTC is no longer recommended as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios*, largely due to the limitations of RPV and the availability of

DOR/TDF/3TC, which has fewer drug–drug interactions and no virologic and immunologic prerequisites. The Panel continues to recommend RPV/TAF/FTC as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (see Table 6b in the Initial Combination Antiretroviral Regimens for People With HIV section), largely to retain an STR option containing an NNRTI and TAF.

- Use of RPV with TAF/FTC **(BII)** should be limited to persons with pre-treatment viral loads <100,000 copies/mL and CD4 counts >200 cells/mm^3.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

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Protease Inhibitor–Based Regimens

Updated: September 12, 2024
Reviewed: September 12, 2024

Table 8d. Characteristics of Protease Inhibitor Options as Initial Antiretroviral Therapy in Certain Clinical Scenarios

Characteristic	DRV
Dosing Frequency	Once daily for persons with no prior PI experience.
PK Boosting	DRV should only be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	• DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes
Adverse Effects	• Skin rash • Increase in serum transaminase • Hyperlipidemia • Diarrhea, nausea
CYP3A4 Drug–Drug Interactions	CYP34A substrate, inhibitor
Other Significant Drug Interactions	N/A

Key: COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; FTC = emtricitabine; N/A = not applicable; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

The U.S. Food and Drug Administration (FDA)–approved protease inhibitors (PIs) include atazanavir (ATV), atazanavirATV/cobicistat (ATV/c), darunavir (DRV), darunavir/cobicistat (DRV/c), fosamprenavir (FPV), indinavir (IDV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and tipranavir (TPV). PI-based regimens using pharmacokinetic (PK) enhancement with either cobicistat (COBI) or RTV (also called PK boosting) increase concentration and prolong the half-lives of the PI. These regimens have demonstrated virologic potency, durability in people who are ART-naive, and a high barrier to resistance. Because LPV/r, fosamprenavir/ritonavir (FPV/r), ATV (with or without a PK enhancer), and saquinavir/ritonavir (SQV/r) have disadvantages—such as greater pill burden, lower efficacy, or increased toxicity—only boosted DRV in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) is recommended as initial therapy in certain clinical situations (see Table 6b in Initial Combination Antiretroviral Regimens for People With HIV).

Because transmitted PI resistance is uncommon, boosted DRV-based regimens are preferred over a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen as an option for treatment initiation before resistance test results are available. In addition, a boosted DRV-based regimen can be used for rapid antiretroviral therapy (ART) initiation, in the setting of acute HIV infection, and as the preferred option while awaiting resistance test results for people with a history of long-acting cabotegravir (CAB-LA) use as pre-exposure prophylaxis (PrEP). Few or no PI mutations are

detected when a patient's first PI-based regimen fails, which is not the case with non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimens and regimens with a first-generation integrase strand transfer inhibitor (INSTI) (e.g., raltegravir or elvitegravir).[1] Because of their high barrier to resistance, PI-based regimens may be useful for people at risk for intermittent therapy because of poor adherence.

DRV requires PK boosting with either RTV or COBI to inhibit the cytochrome P3A4 (CYP3A4) isoenzyme, which may lead to significant drug–drug interactions (see Drug–Drug Interactions). The specific characteristics of DRV are listed in Appendix B, Table 5.

Darunavir/Ritonavir

Efficacy in Clinical Trials

Darunavir/ritonavir (DRV/r) has been studied in several large, randomized controlled trials in people with HIV without prior antiretroviral (ARV) experience. These trials compared DRV/r-based regimens to PI-, INSTI-, or NNRTI-based regimens. Summaries of the results from some key trials are listed below.

- The FLAMINGO study compared DRV/r with dolutegravir (DTG), each administered in combination with two NRTIs—either tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC)—in 488 participants who were ART-naive. The rate of virologic suppression at Week 96 was significantly higher among those who received DTG than in those who received DRV/r. The higher rate of virologic failure observed in the DRV/r group was related primarily to the number of failures among those with a viral load >100,000 copies/mL and secondarily to more drug discontinuations in the DRV/r group.[2]
- The AIDS Clinical Trial Group (ACTG) study A5257 (ARDENT), a large, randomized, open-label trial, compared atazanavir/ritonavir (ATV/r) to DRV/r or raltegravir (RAL) over 96 weeks, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events.[3]
- The DRIVE-FORWARD study compared DRV/r to doravirine (DOR), both administered with two investigator-selected NRTIs, in 769 ART-naive participants. At 48 weeks, DOR was found to be non-inferior to DRV/r, with 80% and 84% of participants achieving HIV RNA levels <50 copies/mL, respectively.[4] At Week 96, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).[4] Rates of virologic failure were low and similar in the DOR and DRV/r groups (9% vs. 11%). Treatment-emergent resistance to any study drug was infrequent, occurring in <1% of participants in both the DOR group (2 of 383) and the DRV/r group (1 of 383).

Adverse Effects

- People with HIV who take DRV/r may develop a skin rash, which is usually mild-to-moderate in severity and self-limited. Treatment discontinuation is necessary on rare occasions when severe rash occurs with fever or elevated transaminases.
- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. Bone mineral density decreased to a greater extent in participants in the ATV/r and DRV/r arms

compared to participants in the RAL arm.[3] The likelihood of developing metabolic syndrome was equivalent among the three arms, although a larger increase in waist circumference was observed at 96 weeks in participants assigned to the RAL arm than in those assigned to the DRV/r arm ($P = 0.023$).[5]

- In the DRIVE-FORWARD study, treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases were observed in fasting low-density lipoprotein cholesterol, triglycerides, non–high-density lipoprotein cholesterol, and total cholesterol compared to the DOR arm.[4]

Other Factors and Considerations

- DRV/r is administered once daily with food in people who are ART-naive.
- DRV has a sulfonamide moiety and should be used with caution in people with severe sulfonamide allergies. In clinical trials, the incidence and severity of rash were similar in participants with and without a history of sulfonamide allergy. Most people with sulfonamide allergy can tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, which may lead to significant interactions with other medications metabolized through this same pathway (see Drug–Drug Interactions).
- Unlike DRV/c, DRV/r may be used in pregnancy.

The Panel's Recommendations

- Based on efficacy and safety data from clinical trials and clinical experience, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies DRV/r with (tenofovir alafenamide [TAF] or TDF) plus (FTC or 3TC) as a *Recommended Initial Regimen for Most People With HIV* who have a history of CAB-LA use as PrEP, pending the results of INSTI genotype testing **(AIII)** (see Table 6a). DRV/r plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/r plus ABC/3TC **(BII)** are also part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios* (see Table 6b and Table 7).

Darunavir/Cobicistat

Efficacy in Clinical Trials

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the single-tablet regimen (STR) DRV/c/TAF/FTC with DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of the study (91% and 88% had HIV RNA <50 copies/mL, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group.[6] At 96 weeks, 85% of participants on the STR maintained HIV RNA levels <50 copies/mL compared to 84% in the DRV/c plus TDF/FTC arm.[7]
- The DIAMOND study evaluated DRV/c/TAF/FTC as an STR in 109 participants in a rapid-initiation model of care. At Week 48, 97 (89%) participants completed the study and 92 (84%) achieved HIV-1 RNA <50 copies/mL by the FDA snapshot analysis. No protocol-defined virologic failures occurred, and incidences of adverse events at least possibly related to study

drugs (33%) were low. No study drug-related serious adverse events occurred, and only one (<1%) participant discontinued because of a study drug-related adverse event.[8]

Adverse Effects

- The most common drug-related adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.

Other Factors and Considerations

- DRV/c 800 mg/150 mg is available as a coformulated boosted PI or as an STR with TAF/FTC 10 mg/200 mg.
- Both DRV and COBI exposures are reduced markedly during the second and third trimesters of pregnancy, and should be avoided if possible.[9] However, if pregnant women with viral suppression while on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended. For further information, please refer to the Perinatal Guidelines.

The Panel's Recommendations

- The Panel recommends DRV/c plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/c plus ABC/3TC **(BII)** as part of *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios*.
- Per product label recommendation, DRV/c plus TDF/FTC **is not recommended** for people with creatinine clearance (CrCl) <70 mL/min, whereas DRV/c plus TAF/FTC **is not recommended** for people with CrCl <30 mL/min.
- For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting ART. If ART is to be started before genotypic testing results are available, DRV/c with (TAF or TDF) plus (FTC or 3TC) can be started **(AIII).**

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

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Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

Updated: September 12, 2024
Reviewed: September 12, 2024

Most of the currently recommended antiretroviral (ARV) regimens for initial therapy consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third active drug. In addition, dolutegravir (DTG)/lamivudine (3TC) is a two-drug, NRTI-limiting regimen that is a recommended option for people with HIV (see Table 6a in Initial Combination Antiretroviral Regimens for People With HIV) and would be preferred over others in situations where it is desirable to avoid abacavir (ABC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF). Several other NRTI-limiting/sparing two-drug regimens have been evaluated in clinical studies, but are not yet recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) due to insufficient evidence. Note that two-drug regimens **are not currently recommended** during pregnancy and tenofovir-sparing regimens **are not recommended** in people with hepatitis B virus (HBV)/HIV coinfection unless another HBV-active drug (i.e., entecavir) is added. Clinicians should refer to HBV/HIV Coinfection for guidance on treatment of people with HBV infection when TAF or TDF cannot be used as part of the ARV regimen.

Strategies Supported by Evidence From Clinical Trials

Dolutegravir/Lamivudine

- In the GEMINI-1 and GEMINI-2 trials, 1,433 antiretroviral therapy (ART)–naive participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive a two-drug regimen of DTG plus 3TC or a three-drug regimen of DTG plus TDF/emtricitabine (FTC). At Week 96, DTG plus 3TC was non-inferior to DTG plus TDF/FTC based on the proportion of participants with viral loads <50 copies/mL (86% in DTG plus 3TC group and 89.5% in DTG plus TDF/FTC group).[1] Virologic nonresponse was uncommon, occurring in 3.1% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No instances of treatment-emergent NRTI or integrase strand transfer inhibitor (INSTI) resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the proportion of participants with HIV RNA <50 copies/mL at Week 96 was lower in the DTG plus 3TC group than in the DTG plus TDF/FTC group; however, the difference was not related to a higher rate of virologic failures in the two-drug group. At Week 144, DTG plus 3TC maintained noninferiority to DTG plus TDF/FTC with 82% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with viral load ≥50 copies/mL was similar between both treatment groups at 3%. There was a lower risk of drug-related adverse events with DTG plus 3TC versus DTG plus TDF/FTC (19.6% vs. 25.0%; relative risk ratio, 0.78; 95% confidence interval, 0.64–0.95).[1]

The Panel's Recommendation

When ABC, TAF, or TDF cannot be used or are not optimal, the Panel recommends DTG/3TC as an initial regimen for people with HIV **(AI)** who—

- Have a viral load ≤500,000 copies/mL,

- Have a genotype available that demonstrates sensitivity to 3TC,
- Do not have a history of long-acting cabotegravir (CAB-LA) use as pre-exposure prophylaxis, *or*
- Have CAB-LA exposure but with documented INSTI sensitivity on genotypic resistance testing.

HBV status must be determined, and if HBV/HIV coinfection is present, another HBV-active drug should be added (see HBV/HIV Coinfection).

Nucleoside-Limiting Regimens With Some Supporting Data but Not Recommended as Initial Therapy

The Panel **does not recommend** the following nucleoside-limiting or nucleoside-sparing regimens for initial therapy due to insufficient clinical trial data.

Darunavir/Ritonavir Plus Lamivudine

- In the ANDES trial, 336 participants were randomized 1:1 to receive open-label, once-daily dual therapy with darunavir/ritonavir (DRV/r) plus 3TC or triple therapy with DRV/r plus TDF/3TC. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies, and 23% of participants had HIV RNA >100,000 copies/mL. At Week 48, 91% of the participants in the dual-therapy group and 93% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL, demonstrating that dual therapy was non-inferior to triple therapy.[2] The rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (87% and 90%, respectively). The Panel **does not recommend** this regimen as initial therapy as the results from this study have not yet been published.

Darunavir/Ritonavir Plus Raltegravir

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily raltegravir (RAL) or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At Week 96, DRV/r plus RAL was non-inferior to DRV/r plus TDF/FTC based on the primary endpoint, the proportion of people with virologic or clinical failure. Among those with baseline CD4 counts <200 cells/mm^3; however, there were more virologic failures in the RAL plus DRV/r arm. A trend towards more failure was also observed among those with pre-treatment HIV RNA ≥100,000 copies/mL.[3] High rates of virologic failure in participants with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.[4,5] The Panel **does not recommend** DRV/r plus RAL as initial ART because of the higher rate of virologic failure in participants with HIV RNA ≥100,000 copies/mL and the higher pill burden of this regimen compared to other Panel-recommended initial ARV regimens.

Darunavir/Ritonavir Plus Rilpivirine

- In a single-arm, open-label pilot study, 36 ART-naive participants without genotypic evidence of resistance to DRV or rilpivirine (RPV) received DRV/r plus RPV for 48 weeks. Half of the participants (18 of 36) had baseline HIV viral loads >100,000 copies/mL. By Week 36, 97% of participants (35 of 36) achieved HIV RNA <50 copies/mL, and by Week 48, all achieved viral

suppression (HIV RNA < 50 copies/mL).[6] The Panel **does not recommend** this regimen as initial ART given the small sample size of the study described above and the lack of comparative data evaluating DRV/r plus RPV as initial therapy for people with HIV.

Long-Acting Injectable Cabotegravir With Rilpivirine

- The long-acting injectable combination of CAB plus RPV (LA CAB/RPV) has not been studied in ART-naive participants. In the Phase 3 trial FLAIR and Phase IIb trial LATTE-2,[7,8] ART-naive participants were first treated with 20 weeks of DTG/ABC/3TC or oral CAB+ABC/3TC, respectively. Study participants who achieved virologic suppression were eligible for randomization to receive LA CAB/RPV every month or to continue oral daily ART. The Panel **does not recommend** the LA CAB/RPV as initial therapy for people with HIV because of the lack of data supporting the efficacy of this combination in people who are ART-naive **(AIII).** People desiring to use LA CAB/RPV early in their treatment history should first attain viral suppression on a recommended regimen before transitioning to LA CAB/RPV. See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for more discussion.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

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Table 9. Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy Listed in Table 6a and Table 6b

Updated: September 12, 2024
Reviewed: September 12, 2024

Note: All drugs within an ARV class are listed in alphabetical order. Information based on Table 6a and Table 6b in the Initial Combination Antiretroviral Regimens for People With HIV section.

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Dual-NRTI	**ABC/3TC**	• Coformulated with DTG • Generic formulations are available for ABC/3TC, ABC, and 3TC.	• May cause life-threatening HSRs in people who test positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with BIC, DRV/c, or RPV • Active against HBV; a recommended dual-NRTI option for people with HBV/HIV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC • Approved for people with eGFR ≥30 mL/min • Can be used in people on chronic hemodialysis	• See text in the NRTI section regarding weight gain with TAF.
	TDF/3TC	• Coformulated with DOR • Generic formulations are available for TDF, 3TC, or TDF/3TC. • Long-term clinical experience • Active against HBV	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
	TDF/FTC	• Active against HBV; a recommended dual-NRTI option for people with HIV/HBV coinfection • TDF is associated with lower lipid levels than TAF.	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters • Osteomalacia has been reported as a consequence of proximal tubulopathy.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy Listed in Table 6a and Table 6b

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
			• Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
Single NRTI	**3TC**	• Coformulated with DTG as STR • Avoids potential toxicities associated with TDF, TAF, ABC	• DTG/3TC **is not recommended** for individuals with HIV RNA >500,000 copies/mL, HBV coinfection unless on another HBV active drug, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
INSTI	**BIC**	• Coformulated with TAF/FTC • Higher barrier to resistance than EVG and RAL • No food requirement	• Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug–drug interactions. • See text in the INSTI section regarding weight gain and INSTI use.
	DTG	• Higher barrier to resistance than EVG or RAL • Coformulated with ABC/3TC and 3TC as STR • No food requirement • Minimal CYP3A4 interactions • Favorable lipid profile	• Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • UGT1A1 substrate; potential for drug interactions (see Table 24d) • Depression and suicidal ideation (rare; usually in people with preexisting psychiatric conditions) • See text in the INSTI section regarding weight gain and INSTI use.
NNRTI	**DOR**	• Coformulated with TDF/3TC • Fewer CNS side effects compared to EFV and RPV • No food requirement	• Shorter-term clinical experience than with RPV • Potential for CYP450 drug interactions (see Tables 24b, 25a, and 25b) • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy Listed in Table 6a and Table 6b

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)

	RPV	• Coformulated with TAF/FTC	• **Not recommended** in people with pre-ART HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3 because of higher rate of virologic failure in these people.
			• Depression and suicidality
			• QTc interval prolongation; consider using an alternative to RPV in people taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.
			• Rash
			• Transmitted resistance is more common than with PIs and INSTIs.
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and two NRTIs
			• Potential for CYP450 drug interactions (see Tables 24b and 25a)
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption
			  ○ Contraindicated with PPIs.
			  ○ Use with H2 antagonists or antacids with caution (see Table 24a for detailed dosing information).

PI	**DRV/c** or **DRV/r**	• Higher barrier to resistance than NNRTIs • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs.	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 24a) • Increased CV risk reported in one observational cohort study[a] • Hepatotoxicity has been reported, especially in those with preexisting liver disease.
	DRV/c Specific considerations	• Coformulated as DRV/c and DRV/c/TAF/FTC	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF **is not recommended** in people with CrCl <70 mL/min.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy Listed in Table 6a and Table 6b

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
			• COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI should be avoided in pregnancy because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended.

[a] D:A:D international prospective multicohort study[1]

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; GI = gastrointestinal; H2 = histamine 2; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; Mg = magnesium; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase

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Management of People With HIV and Antiretroviral Therapy Experience

Virologic Failure

Updated: September 12, 2024
Reviewed: September 12, 2024

Key Considerations and Recommendations
• Assessing and managing a person with HIV who is experiencing antiretroviral therapy (ART) failure can be complex. Expert advice can be critical and should be sought in many instances. • Evaluation of virologic failure should include an assessment of ART adherence, drug–drug and drug–food interactions, drug tolerability, HIV RNA level and CD4 T lymphocyte (CD4) cell count trends over time, ART history, and prior and current drug-resistance test results. • Drug-resistance testing should be performed while the person is taking the failing antiretroviral (ARV) regimen **(AI)** or within 4 weeks of discontinuing a non–long-acting ARV regimen **(AII).** If more than 4 weeks have elapsed since non–long-acting ARV regimens were discontinued, resistance testing still can provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII).** • For people who previously received long-acting (LA) cabotegravir (CAB) plus rilpivirine (RPV), or LA CAB/RPV, and present with virologic failure, resistance testing (including integrase strand transfer inhibitor [INSTI] genotypic testing) should be performed regardless of the time since the last dose of LA CAB/RPV **(AIII).** • The goal of treatment for people with HIV with drug resistance who are experiencing virologic failure is to establish virologic suppression (i.e., HIV RNA levels below the lower limits of detection of currently used assays) **(AI).** • A new ARV regimen should preferably include two fully active drugs if at least one has a high resistance barrier, such as a second-generation INSTI or a boosted protease inhibitor (PI) **(AI).** • A new ARV regimen can also include a second-generation INSTI (i.e., dolutegravir [DTG]) plus a boosted PI (preferably boosted darunavir) without nucleoside reverse transcriptase inhibitors (NRTIs) if both are fully active **(AI)**. • If the above two options are not feasible, a new ARV regimen that includes at least one drug with a high resistance barrier plus two partially active NRTIs—particularly tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) with lamivudine (3TC) or emtricitabine (FTC)—can also be considered, although this is a less well-defined strategy and is based on an extrapolation of existing data. Caution with close monitoring of virologic response is advised **(BII),** as discussed below**.** • If no fully active drug with a high resistance barrier is available, every effort should be made to include three fully active drugs in the new ARV regimen **(AI).** • In general, adding a single ARV drug to a virologically failing regimen **is not recommended,** because this would rarely result in full virologic suppression and may risk the development of resistance to all drugs in the regimen **(BII).** • In some rare instances, it might not be possible to achieve maximal virologic suppression in people with HIV who are highly ART-experienced and have extensive drug resistance. In this case, ART should be continued **(AI)** with regimens that are designed to maintain CD4 counts, preserve treatment options, delay clinical progression, and minimize toxicity. • When it is not possible to construct a viable suppressive regimen for a person with multidrug-resistant HIV, the clinician should consider enrolling the person in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.

- In people with HIV and virologic failure, it is crucial to provide continuous adherence support before and after ARV regimen changes.
- When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, the person should remain on an ARV agent that is active against HBV and has a high resistance barrier to HBV (i.e., TAF, TDF, or entecavir) to avoid HBV rebound and hepatocellular damage **(AII)** (see Hepatitis B Virus/HIV Coinfection for more information).
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 count, and an increase in the risk of clinical progression. Therefore, discontinuing or interrupting ART **is not recommended** in the setting of virologic failure **(AI).**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral (ARV) regimens that are currently recommended for initial therapy in people with HIV have a high likelihood of achieving and maintaining plasma HIV RNA levels that are below the lower limits of detection (LLOD) of currently used assays (see Initial Combination Antiretroviral Regimens for People With HIV). People on antiretroviral therapy (ART) who do not achieve this treatment goal or who experience virologic rebound can develop resistance mutations to one or more components of their ARV regimen with possible cross-resistance to other ARVs. Adherence to ARV regimens can be challenging for some people with HIV, and poor adherence can result in detectable HIV RNA levels. The extent of drug resistance varies based on ARV treatment history, with some people having minimal or no resistance and others with extensive resistance. Managing people with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in people on ART and discusses strategies to manage ART in these individuals.

Virologic Response Definitions

The following definitions are used in this section to describe the different levels of virologic response to ART.

- **Virologic suppression:** A confirmed HIV RNA level below the LLOD of available assays.
- **Virologic failure:** The inability to achieve or maintain suppression of viral replication to HIV RNA level <200 copies/mL.
- **Incomplete virologic response:** Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a person who has not yet had documented virologic suppression on that regimen. A person's baseline HIV RNA level may affect the time course of response, and some regimens may take longer than others to suppress HIV RNA levels.
- **Virologic rebound:** After virologic suppression, confirmed HIV RNA level ≥200 copies/mL.
- **Virologic blip:** After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.
- **Low-level viremia:** Confirmed HIV RNA level above the LLOD but <200 copies/mL.

Antiretroviral Therapy Goals and Presence of Viremia While on Antiretroviral Therapy

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations cannot emerge. Although not conclusive, the evidence suggests that selection of drug-resistance mutations does not occur in people with HIV RNA levels that are persistently suppressed below the LLOD of current assays.[1]

Virologic blips are not usually associated with subsequent virologic failure.[2] In contrast, there is controversy regarding the clinical implications of low-level viremia, i.e., persistent HIV RNA levels between the LLOD and <200 copies/mL in people on ART. Viremia at this threshold is detected with some frequency by commonly used real-time polymerase chain reaction (PCR) assays, which are more sensitive than the PCR-based HIV RNA platforms used in the past.[3-5] Several retrospective studies support the supposition that virologic failure is more likely to occur in people with HIV RNA levels ≥200 copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.[6-8] However, other studies have suggested that detectable viremia at <200 copies/mL can be predictive of virologic failure[9] and can be associated with the evolution of drug resistance[10] and non-AIDS morbidities.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[12] This association is particularly common with HIV RNA levels >500 copies/mL.[13] Therefore, people who have persistent HIV RNA levels ≥200 copies/mL are considered to be experiencing virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations.[14,15] Current ARVs are easier to tolerate and have less pill burden, which may improve adherence.[16-18] Virologic failure may be associated with a variety of factors, including the following:

HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus that may or may not be documented by current or past drug-resistance test results
- Prior ARV treatment failure
- Innate drug resistance to prescribed ARV drugs
- Higher pre-treatment HIV RNA levels (e.g., HIV RNA >100,000 copies/mL; some regimens may be less effective at higher levels)

Antiretroviral Regimen–Related Factors

- Suboptimal pharmacokinetics (PK) (e.g., variable absorption, metabolism, penetration into reservoirs)
- Suboptimal virologic potency

- Low barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual–nucleoside reverse transcriptase inhibitor [NRTI] therapy, or the sequential introduction of drugs)
- Food requirements
- Drug–drug interactions with concomitant medications, which may reduce concentrations of the ARV drugs
- Adverse drug effects
- High pill burden and/or dosing frequency
- Prescription (prescribing or dispensing) errors

Social and Adherence-Related Factors

Note: Each of the social and adherence-related factors listed below are discussed in the Adherence to the Continuum of Care section.

- Active substance use, mental health disorders, or neurocognitive impairment
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost and affordability of ARV drugs, which may affect the ability to access or continue therapy (see the Cost Considerations and Antiretroviral Therapy section)

Managing People With HIV and Virologic Failure

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above factors could have been the cause(s) of failure is indicated. The causes of virologic failure can usually be identified but may not be obvious in some cases. Distinguishing among the causes of virologic failure is important, because the approaches to subsequent therapy may differ, depending on the cause. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be taken to improve virologic outcomes. If a new ARV regimen is needed, approaches to designing a new regimen are discussed below.

Key Factors to Consider When Designing a New Antiretroviral Regimen After Virologic Failure

General Principles on Antiretroviral Use in Virologic Failure

- When designing a new ARV regimen for a person with virologic failure, it is important to consider the factors outlined above on causes of virologic failure and, if possible, consider better tolerated and adherence-friendly regimens.
- A new ARV regimen should be selected based on ART history, current and previous drug-resistance test results, and whether a fully susceptible ARV drug with a high barrier to resistance and other fully active drugs are available.[9,19-31]

- ARV drugs with a high barrier to resistance are those in which emergent resistance is uncommon in people experiencing virologic failure. These include boosted darunavir (DRV), dolutegravir (DTG), and bictegravir (BIC).
- Fully active drugs may include—
  - Drugs in classes for which the person has not previously selected for drug-resistant virus.
  - Newer drugs in existing drug classes that are predicted to be fully active against HIV isolates despite the presence of resistance mutations for some drugs in the same drug class. For example, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) etravirine and possibly doravirine (DOR), the protease inhibitor DRV, and the integrase strand transfer inhibitors (INSTIs) DTG and BIC. However, clinical data supporting the use of DOR or BIC in the setting of virologic failure are limited.
  - Drugs with novel mechanisms of action that the person with HIV has not received before, such as the post-attachment inhibitor ibalizumab (IBA), the gp120 attachment inhibitor fostemsavir (FTR), the capsid inhibitor lenacapavir (LEN), the fusion inhibitor enfuvirtide (T-20), or the CCR5 antagonist maraviroc (MVC) in people with no detectable CXCR4-using virus.
- ARV drugs with partial activity are those predicted to have antiviral activity but to a lesser extent than when there is no underlying drug resistance.
- Administering a drug that a person has never used does not ensure that the drug will be fully or partially active; the potential exists for cross-resistance among drugs from the same class.
- Discontinuing or briefly interrupting therapy in a person with viremia **is not recommended** because it may increase HIV RNA levels, decrease CD4 T lymphocyte (CD4) cell count, and increase the risk of clinical progression **(AI)**[32,33] (see Discontinuation or Interruption of Antiretroviral Therapy).
- The presence of preexisting (transmitted) drug resistance also may lead to virologic failure.[34,35]

Drug-Resistance Testing to Guide New Antiretroviral Regimens

- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that drug-resistance testing should be used to guide ARV regimen design and should be performed while the person with HIV is still taking the failing regimen **(AI)** or within 4 weeks of discontinuation of a non–long-acting regimen **(AII).** If more than 4 weeks have elapsed since discontinuation of a non–long-acting regimen, drug-resistance testing still may provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII).**
- Drug-resistance testing is recommended in persons with confirmed virologic failure, i.e., HIV RNA repeatedly >200 copies/mL (**AI** for >1,000 copies/mL, **AIII** for 501–1,000 copies/mL, **CIII** for confirmed 201–500 copies/mL), although at low HIV RNA levels, testing may be difficult to obtain outside of a research setting. In persons with HIV RNA >200 copies/mL but <500 copies/mL, testing may be unsuccessful, but it still should be considered.
- Drug resistance is cumulative, meaning that once a mutation is detected in a resistance assay, it should be considered present in that person's HIV thereafter (this is sometimes referred to as "archived" resistance), regardless of whether it appears on subsequent drug-resistance assays.

Thus, clinicians should evaluate the extent of drug resistance, taking into account all of the person's ART history and, importantly, prior genotypic- or phenotypic-resistance test results.

- Activity of ART based on current and cumulative genotypic mutations can be estimated by tools and interpretation algorithms, such as the Stanford University HIV Drug-Resistance Database. Also see Drug-Resistance Testing.
- Some drug-resistance assays only detect resistance to NRTIs, NNRTIs, or protease inhibitors (PIs); INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in people who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for people who experience failure on a fusion inhibitor **(AII),** and viral tropism tests for people who experience failure on a CCR5 antagonist **(BIII)** are also available. There is currently no commercially available resistance test for IBA, FTR, or LEN (see Drug-Resistance Testing).

Strategies for New Antiretroviral Regimen Design

- A new ARV regimen should preferably include two fully active drugs if at least one has a high resistance barrier, such as a second-generation INSTI or a boosted PI **(AI).**[36]
- A new ARV regimen can also include a second-generation INSTI (e.g., DTG) plus a boosted PI (preferably boosted DRV) without NRTIs if both are fully active **(AI);**[37-41] see more detailed discussion in *Managing Virologic Failure in Different Clinical Scenarios* below. If this regimen is used in people with hepatitis B virus (HBV)/HIV coinfection, an HBV-active drug with a high barrier to resistance (e.g., tenofovir alafenamide [TAF], tenofovir disoproxil fumarate [TDF], or entecavir) should be continued or started to avoid HBV rebound and hepatocellular damage.
- If the above two options are not feasible, a new ARV regimen can also include a fully active drug with a high resistance barrier plus two partially active NRTIs—particularly TAF or TDF with lamivudine (3TC) or emtricitabine (FTC)—though this is less well-defined and close monitoring is advised **(BII);** this is discussed in more detail in *Managing Virologic Failure in Different Clinical Scenarios* below.[36,37,42,43]
- If no fully active drug with a high resistance barrier is available, every effort should be made to include three fully active drugs in the regimen **(AI).** See the clinical scenarios below for further guidance on the number of fully active drugs a regimen should contain.
- Despite the presence of drug-resistance mutations, some ARV drugs in the regimen may still have partial activity against the person's HIV and may be retained as part of a salvage regimen. These drugs may include NRTIs, PIs, and second-generation INSTIs, although dosing of some drugs (e.g., DRV and DTG) may need to be increased when treating people with relevant resistance mutations to achieve drug concentrations necessary to be at least partially active against a less sensitive virus.[44-46]
- In contrast, other agents in which resistance may be expected should be discontinued, because their continued use is unlikely to contribute to virologic suppression. These drugs include NNRTIs (especially efavirenz, nevirapine, and rilpivirine [RPV]), the first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG), and T-20.[47-49]
- Long-acting (LA) cabotegravir (CAB)/rilpivirine (RPV) is currently approved as a complete ART regimen for individuals engaged in care who have good adherence to an oral regimen, sustained undetectable HIV RNA levels for >3 months, no known or suspected resistance to

either drug, and no active HBV infection. To date, no large or randomized clinical trials have been published using any INSTI plus NNRTI, including LA CAB/RPV, as a complete regimen for people without viral suppression. However, a few small observational studies have shown that people with viremia despite intensive efforts on oral ART, without resistance to CAB or RPV, can achieve viral suppression with LA CAB/RPV when intensive supportive services are available.[50-53] If considering LA CAB/RPV in this population, it is important to note that data are limited, and this is not an approved indication of the regimen. If the regimen is used in people with inconsistent adherence and virologic failure, there is a high likelihood of developing acquired resistance to CAB and/or RPV, which might limit future treatment options. The approaches and considerations for the use of LA CAB/RPV in people with viremia is further outlined below.

- When changing an ARV regimen in a person with HBV/HIV coinfection, ARV drugs that are active against HBV (especially TAF or TDF) should be continued as part of the new regimen or, if not possible, entecavir should be initiated **(AII).** Using 3TC or FTC as the only drug with HBV activity in a regimen **is not recommended (AII)** because HBV resistance to these drugs can emerge. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage (see Hepatitis B Virus/HIV Coinfection).
- Virologic responses should be closely monitored after regimen switch (e.g., HIV RNA level testing performed within 4 to 8 weeks), with prompt drug-resistance testing if virologic response is inadequate.

Managing Virologic Failure in Individuals With Different Levels of Viremia

People with HIV and detectable HIV RNA levels while on ART comprise a heterogeneous group of individuals with different ART exposure histories, degrees of drug resistance, durations of virologic failure, and levels of plasma viremia. Management strategies should be individualized. The first steps are to confirm the level of HIV viremia and to assess and address adherence and potential drug–drug interactions (including interactions with over-the-counter products and supplements) and drug–food interactions. Some general approaches based on the level of viremia are addressed below.

- **Low-level viremia (HIV RNA above the LLOD and <200 copies/mL):** People who have these HIV RNA levels do not typically require a change in treatment **(AII).**[4] Although there is no consensus on how to manage these individuals, the risk that drug resistance will emerge is believed to be relatively low. Therefore, these individuals should continue their current regimens and have their HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future **(AIII).**
- **HIV RNA ≥200 copies/mL and <1,000 copies/mL:** In contrast to people with detectable HIV RNA levels that are persistently <200 copies/mL, people with levels that are persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.[6,7] People who have persistent plasma HIV RNA levels in the range of 200 copies/mL to 1,000 copies/mL are considered to be experiencing virologic failure, and drug-resistance testing should be attempted, particularly in people with HIV RNA levels >500 copies/mL (at <500 copies/mL, testing may not be possible for technical reasons). Management approaches should be the same as for people with HIV RNA >1,000 copies/mL (as outlined below). When drug-resistance testing cannot be performed because of low HIV RNA levels, the decision of whether to empirically change ARV drugs should be made on a case-by-case basis, taking into account whether a new regimen that is expected to fully suppress viremia

can be constructed. If genotypic-resistance test results cannot be obtained because of low HIV RNA levels, proviral DNA genotypic testing may be considered. Results from this test should be interpreted with caution because these assays might miss some or all previously existing drug-resistance mutations. However, mutations that are detected using proviral DNA genotypic testing may be significant and can affect the effectiveness of future regimens (see Drug-Resistance Testing).

- **HIV RNA ≥1,000 copies/mL and no drug-resistance mutations identified using current or previous genotypic-resistance test results:** This scenario is almost always associated with suboptimal adherence. A thorough assessment should be conducted to evaluate the level of adherence, identify and address the underlying cause(s) for incomplete adherence and, if possible, simplify the regimen (e.g., decrease pill count, simplify food requirement or dosing frequency; see Adherence to the Continuum of Care). Assessment includes the following:
  - Assessing the person's access to ART, including access to pharmacy, refills, and copays or patient assistance programs, and seeking assistance to overcome any barriers to consistent access to ART.
  - Assessing social determinants that may impact adherence (e.g., substance use, unstable housing, mental health challenges, etc.).
  - Assessing the person's tolerance of the current ARV regimen and the severity and duration of side effects if intolerance is a concern, while considering that even minor side effects can affect adherence.
  - Addressing intolerance by treating symptoms (e.g., with antiemetics or antidiarrheals), switching one ARV agent in a regimen to another agent in the same drug class, or switching from one drug class to another class (e.g., from an NNRTI to a PI or an INSTI; see Adverse Effects of Antiretroviral Agents).
  - Reviewing food requirements for each medication and assessing whether the person adheres to the requirements.
  - Assessing whether a recent history of gastrointestinal symptoms (e.g., vomiting, diarrhea) may result in short-term malabsorption.
  - Reviewing concomitant medications (including over-the-counter medications and dietary supplements) for possible adverse drug–drug interactions (consult Drug–Drug Interactions and Tables 24a through 25b for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
  - Considering therapeutic drug monitoring if PK drug–drug interactions (e.g., when used with rifamycin) or impaired drug absorption (e.g., using polyvalent cations with an INSTI) leading to decreased ARV drug exposure is suspected.
  - Considering the timing of the drug-resistance test (e.g., was the person mostly or completely nonadherent to oral ART for >4 weeks before testing?) (see Drug-Resistance Testing).
  - After a thorough assessment, the following approaches may be considered:
    - If the current regimen is well tolerated, with no significant drug–drug or drug–food interactions, it is reasonable to continue the same regimen while focusing on improving adherence.

  - If the agents are poorly tolerated or have important drug–drug or drug–food interactions, changing the regimen to an equally effective but more tolerable regimen should be considered.
  - HIV RNA level testing should be repeated 4 to 8 weeks after treatment adherence is encouraged or treatment is modified **(AII);** if RNA levels remain >200 copies/mL, genotypic drug-resistance testing should be performed to determine whether a resistant viral strain has emerged (**AI** for >1,000 copies/mL, **AIII** for 501–1,000 copies/mL, **CIII** for 201–500 copies/mL), though at low RNA levels, testing may be difficult to obtain outside of a research setting.

- **HIV RNA >1,000 copies/mL and drug resistance identified:** If new or previously detected resistance mutations compromise the regimen, the regimen should be modified as soon as possible to avoid progressive accumulation of resistance mutations.[54] In addition, several studies have shown that virologic responses to new and fully active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 counts at the time of regimen changes; thus, the change is best done before viremia worsens or before CD4 count declines.[9,55] The availability of newer ARV drugs, including some with new mechanisms of action, makes it possible to suppress HIV RNA levels to below the LLOD in most people with HIV. The options in this setting depend on the extent of drug resistance and are addressed in the clinical scenarios outlined below.

Managing Virologic Failure in Different Clinical Scenarios

Note: See Table 10 below for a summary of these recommendations.

Virologic Failure on the First Antiretroviral Regimen

The Panel recommends that drug-resistance testing should be performed upon treatment failure to inform regimen design **(AI).**

NNRTI plus NRTI regimen failure: Although an NNRTI plus NRTI regimen is no longer considered a preferred first-line ART option in treatment guidelines, data from clinical trials comparing different ARV regimens after NNRTI plus NRTI failure provide the most robust evidence to inform second-line treatment strategies and, therefore, are included here.

In this setting, people with HIV often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to 3TC and FTC. Additional NRTI mutations also may be present. Below are some treatment options.

- **Second-generation INSTI (BIC or DTG) plus NRTIs:** The Panel recommends that fully active DTG plus two NRTIs, at least one of which is fully active, can be a treatment option after failure of a first-line NNRTI-based therapy **(AI).** BIC, which is available only in a combination pill with FTC/TAF, also has a high resistance barrier and may have similar activity to that of DTG in this setting, and is also an option **(AIII);** however, no clinical trial data for this strategy with BIC is available. If at least one fully active NRTI cannot be assured and a clinician wants to avoid using a boosted PI or a drug from other classes, a regimen that includes fully active DTG plus two NRTIs that are estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered, with caution and close monitoring of viral response, as further discussed below **(BII).**

In the DAWNING trial, participants from 13 countries who experienced virologic failure while on a first-line NNRTI-based regimen were randomized to receive either lopinavir/ritonavir(LPV/r) or DTG, each with two NRTIs, one of which had to be fully active based on real-time drug-resistance testing. The study was stopped early after an interim analysis showed that the DTG arm was superior to the LPV/r arm. The superiority of DTG was somewhat counterbalanced by the finding that 2 of 11 participants in the DTG arm who met virologic withdrawal criteria selected for INSTI resistance, with no PI resistance selected for in the LPV/r arm.[36]

In the NADIA trial, participants in Uganda, Kenya, and Zimbabwe who experienced virologic failure while on a first-line NNRTI plus TDF and 3TC or FTC were randomized to receive either darunavir/ritonavir (DRV/r) or DTG, each with 3TC; participants were assigned by a second randomization to receive a third ARV, either TDF or zidovudine (ZDV). Unlike the DAWNING study, full activity of the NRTIs based on genotype testing at the time of switch was not required.[42,43] The primary study outcome was virologic suppression <400 copies/mL; at 48 and 96 weeks, >85% of participants had HIV RNA levels <400 copies/mL in all arms, and the DTG-based regimens were non-inferior to the DRV/r-based regimens. However, at 96 weeks, 9 of 235 (4%) participants in the DTG group developed DTG resistance. This represented 45% of participants in the DTG group with HIV RNA levels >400 copies/mL, six of whom were assigned to ZDV. In contrast, no PI resistance was selected for in the DRV/r group. When comparing TDF with ZDV, the two NRTIs demonstrated virologic suppression noninferiority at 48 weeks, but TDF was superior to ZDV at 96 weeks. These results included 84 of 92 (91%) participants in the DTG group who had virologic suppression <400 copies/mL despite no predicted active NRTIs at the time of failure of first-line NNRTI-based regimens, and a large proportion of this group had the K65R and M184V/I mutations. Individual-level drug-resistance data would have enabled further examination of specific mutation patterns and their association with patient characteristics and treatment outcomes. Although such data are not available, these results suggest that ZDV should not be used over TDF in a public health approach. The decision to use DTG or DRV/r without another fully active drug should balance the overall efficacy data of these regimens, with considerations for potential emergent drug resistance, drug–drug interactions, convenience, and tolerability. The results from these studies should be interpreted with caution, as individual-level drug-resistance data and their linkage to patient characteristics and outcomes were not available, thus preventing full interpretation of these results. Additionally, these results may not be generalizable to settings and populations outside of the trials due to differences in geography, HIV-1 subtype, study population, ART availability, and treatment monitoring practice.

- **Boosted PI plus NRTIs:** The Panel recommends that a boosted PI (preferably boosted DRV) plus two NRTIs, at least one of which is fully active, can be an option after failure of a first-line NNRTI-based therapy **(AI).** However, if full activity of at least one NRTI in the regimen cannot be assured, fully active boosted DRV plus two NRTIs estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered, with close monitoring **(BII).** Notably, boosted PIs as monotherapy **are not recommended (AI).**[37,39,40,42,43,56]

  Several large, randomized controlled trials (primarily conducted in resource-limited settings where NNRTI-based regimens have been used as first-line therapy) have explored different second-line regimen options. The studies found that regimens that contained LPV/r or DRV/r plus at least two NRTIs were as effective as regimens that contained LPV/r plus RAL or DTG plus two NRTIs. Participants in some of these studies did not undergo drug-resistance testing before randomization. In the NADIA trial (summarized above), virologic efficacy of DTG and DRV/r-based regimens were non-inferior at 48 and 96 weeks, with TDF being non-inferior at

48 weeks and superior at 96 weeks compared with ZDV. Although there were nine participants in the DTG group who developed DTG resistance (six on ZDV and three on TDF), no participant in the DRV/r group developed PI resistance. Additionally, 74 of 80 (93%) participants in the DRV/r group had virologic suppression <400 copies/mL at 96 weeks despite no predicted active NRTIs at the time of failure of first-line NNRTI-based regimens. As outlined above in the discussion about second-generation INSTI plus no estimated fully active NRTIs based on current drug-resistance algorithms, these results should be interpreted with caution within, and particularly beyond, the study populations and settings.

- **Boosted PI plus an INSTI:** The Panel recommends that boosted DRV plus DTG, both with high barriers to resistance, should be the preferred boosted PI plus INSTI option **(AI).** In a setting where a two-drug boosted PI and INSTI combination are being considered and both boosted DRV and DTG cannot be used, LPV/r plus RAL can be a treatment option for those who experienced virologic failure on an NNRTI-based regimen **(CI).**

  D^2EFT is an open-label multinational randomized controlled trial that assessed the efficacies of DRV/r plus DTG versus DTG plus two NRTIs versus standard of care (DRV/r plus two NRTIs) for participants with first-line failure of an NNRTI-based regimen.[41] In D^2EFT, TDF plus 3TC or FTC were the NRTIs used. At 48 weeks, the proportion of participants who achieved HIV RNA <50 copies/mL was 84% for the DRV/r + DTG arm, 75% for the DRV/r plus two NRTI arm, and 78% for the DTG plus two NRTI arm, showing that the DRV/r + DTG arm was non-inferior to the other two regimens, with more participants achieving viral suppression. Several other small retrospective studies have found that a regimen of boosted DRV plus DTG is effective in achieving viral suppression in people with documented resistance to multiple drug classes.[57-59] Three randomized controlled trials have found that a regimen that consisted of LPV/r plus RAL can be as effective as LPV/r plus at least two NRTIs as second-line therapy for people who failed first-line ART (mostly with an NNRTI-based regimen).[37,39,40]

  If this regimen is used in people with HBV coinfection, an HBV-active drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir) should be continued or started to avoid HBV rebound and hepatocellular damage.

Boosted PI plus NRTI regimen failure: In this scenario, because boosted PI has a high barrier to resistance, most people will have either no resistance or resistance that is limited to 3TC and FTC, though additional NRTI mutations also may be present.[60,61] Failure in this setting is often attributed to poor adherence, drug–drug interactions, or drug–food interactions. Below are some management options.

- **Switch to a second-generation INSTI plus NRTIs regimen:** Second-generation INSTIs have increasingly become preferred options over boosted PIs due to lower drug–drug interaction potential, improved tolerability, comparable efficacy, and a high barrier to resistance. Therefore, consideration should be given to switching to DTG or possibly BIC plus two NRTIs (if at least one of them is fully active) **(AIII).** If only one of the NRTIs is fully active or if adherence is a concern, DTG is currently preferred over BIC **(AIII).** If full activity of at least one NRTI in the regimen cannot be assured, DTG plus two NRTIs estimated to be only partially active based on current drug-resistance algorithms (particularly TAF or TDF with 3TC or FTC) can be considered **(CIII).** As outlined above, results from studies that may suggest such extrapolations should be interpreted with caution, as they did not involve failure of first-line boosted PI plus NRTIs regimens and as individual-level drug-resistance data and their linkage to patient characteristics and outcomes were not available, thus preventing full interpretation of these results. Additionally, these results may not be generalizable to settings and populations

outside of the trials due to differences in geography, HIV-1 subtype, patient population, ART availability, and treatment monitoring practice.

- **Maintain the same regimen:** A systematic review of multiple randomized trials that investigated the failures of first-line ritonavir-boosted PI-based regimens showed that taking actions to improve adherence to the original regimen is as effective as changing to new regimens with or without drugs from new classes **(AII).**[62] If the regimen is well tolerated with no concerns about drug–drug or drug–food interactions or drug resistance, then the regimen can be continued with adherence support and viral monitoring.
- **Switch to another PI-based regimen:** If a regimen with an INSTI plus two NRTIs is not an option and poor tolerability is contributing to virologic failure, the regimen can be modified with a different boosted PI that has no evidence for cross-resistance, plus a second-generation INSTI **(AIII),** or plus two NRTIs (at least one of which is fully active) **(AIII).** If full activity of at least one NRTI in the regimen cannot be assured, another fully active boosted PI plus two NRTIs estimated to be only partially active (particularly TAF or TDF with 3TC or FTC) can be considered, with close monitoring of viral response **(BIII).**

INSTI plus NRTI regimen failure: Virologic failure in people on a regimen that consists of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC or FTC (with/without additional NRTI mutations) and, possibly, the INSTI.[63] Viruses with EVG or RAL resistance often remain susceptible to DTG and BIC.[55] However, in the presence of certain INSTI mutations, DTG dose should be increased from once daily to twice daily.[44] The effective dose of BIC in these situations is unknown. In contrast, in clinical trials, people who experienced virologic failure while receiving DTG or BIC plus two NRTIs as first-line therapy were unlikely to develop resistance to DTG or BIC.[63-65] No existing clinical trial data guide therapy for first-line INSTI failures; therefore, treatment strategy should be based on drug-resistance test results and the potential potency of the next regimen. Below are some treatment options, based on drug-resistance pattern considerations.

- **Virologic failure without any resistance mutations:** The person with HIV should be managed as outlined above in the section on virologic failure without drug resistance.
- **Virologic failure without INSTI resistance:** The regimen can be modified to one of the following:
  - A boosted PI plus two NRTIs (preferably at least one of which is fully active) **(AIII);** *or*
  - DTG, or likely BIC, plus two NRTIs (preferably at least one of which is fully active) **(AIII);** *or*
  - A boosted PI plus DTG **(AIII).**
- **Virologic failure with resistance to RAL and/or EVG but susceptibility to DTG:** The regimen can be modified to one of the following:
  - A boosted PI plus two NRTIs (preferably at least one of which is fully active) **(AIII);** *or*
  - DTG (twice daily) plus two NRTIs (at least one of which is fully active) **(BIII);** *or*
  - DTG (twice daily) plus a boosted PI **(AIII).**

Although BIC has a high resistance barrier, there are no data on whether the current BIC dose is efficacious in settings with RAL or EVG resistance and, therefore, it **is not currently recommended (BIII).**

INSTI plus NNRTI regimen failure: Virologic failure in people on a regimen that consists of an INSTI (e.g., DTG or CAB) plus an NNRTI (e.g., RPV) may be associated with resistance to one or both of the medications in the regimen.[66,67] Experience to guide therapy upon failure of these regimens is limited. Therefore, treatment strategies should be based on past treatment history, drug-resistance test results, and the potential potency of the next regimen, based on the guidance provided above.

Second-Line Regimen Failure and Beyond

Drug resistance with fully active commonly used ARV drug options: Using a person's complete ARV treatment history and drug-resistance data, a clinician can decide whether to include a fully active boosted PI or INSTI in future regimens. For example, those who have no documented PI resistance and who have never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. Similarly, people who have no documented INSTI resistance and who have never been treated with an INSTI are likely to have virus susceptible to DTG or BIC. In this setting, virologic suppression should be achievable using a boosted PI plus either two NRTIs (preferably at least one of which is fully active), a boosted PI plus an active INSTI, or DTG or BIC plus two NRTIs (preferably at least one of which is fully active). Drugs should be selected based on the likelihood that they will be fully active, as determined by the person's treatment history, past and present drug-resistance testing, and tropism testing if a CCR5 antagonist is being considered.

Multidrug resistance without fully active commonly used ARV drug options: Use of currently available ARV drugs has resulted in a dramatic decline in the number of people with HIV who have few treatment options because of multiclass drug resistance.[68,69] Despite this progress, some people have experienced toxicities with and/or developed resistance to most currently available commonly used ARV drugs. Maximal virologic suppression should remain the goal; however, if it cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens.

Consensus on the optimal management of people with multidrug-resistant HIV is lacking. If neither a fully active boosted PI nor a second-generation INSTI (e.g., DTG or BIC) is available, the new regimen should include at least two, and preferably three, fully active agents. If less than three fully active drugs are available, the regimen should include as many fully active drugs as possible, along with potentially partially active agents **(BII).** If resistance to NNRTIs, T-20, MVC, BIC, DTG, CAB, EVG, or RAL are identified, there is rarely a reason to continue using these drugs, because there is little evidence that keeping them in the regimen helps delay disease progression **(BII).** Moreover, continuing these drugs (in particular, early-generation INSTIs) may allow selection of additional resistance mutations and development of within-class cross-resistance that may limit future treatment options. It should be noted that even partial virologic suppression of HIV RNA to >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit.[68,70] Cohort studies provide evidence that even in the presence of viremia and no improvement in CD4 count, continuing ART reduces the risk of disease progression.[71] Other cohort studies suggest that even modest reductions in HIV RNA levels continue to confer immunologic and clinical benefits.[72,73] However, these potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations. In general, adding a single, fully active ARV drug to the regimen **is not recommended** because of the risk of rapid development of resistance **(BII).**

People with HIV and ongoing detectable viremia who lack sufficient treatment options due to an inability to construct a fully suppressive regimen with common ARVs may be candidates for the

first-in-class CD4 post-attachment inhibitor IBA,[74] the gp120-directed attachment inhibitor FTR,[75] and/or the capsid inhibitor LEN.[76]

- **Ibalizumab (IBA)** is a long-acting CD4 post-attachment inhibitor that is given intravenously every 2 weeks. A single-arm, multicenter clinical trial enrolled 40 heavily ART-experienced participants who had multidrug-resistant HIV-1 and who were experiencing virologic failure on an ARV regimen. Subjects received intravenous IBA infusions every 2 weeks, in addition to an optimized background regimen (OBR) that included at least one additional agent to which the subject's virus was susceptible. At Week 24, 43% of participants achieved HIV RNA <50 copies/mL, and 50% achieved HIV RNA <200 copies/mL.[77] Of the 27 participants who continued to the 48-week follow-up study, 59% and 63% had HIV RNA <50 copies/mL and <200 copies/mL, respectively. All 15 participants who had HIV RNA <50 copies/mL at Week 24 maintained virologic suppression up to Week 48.[78]
- **Fostemsavir (FTR)** is a gp120 attachment inhibitor that is given orally twice daily. A Phase 3 multicenter trial enrolled 371 heavily ART-experienced participants who had multidrug-resistant HIV-1 and who were experiencing virologic failure. Participants were enrolled into two cohorts, according to their remaining treatment options. The randomized cohort (n = 272) included those with at least one fully active approved ARV drug in at least one but no more than two classes. These individuals were randomized to FTR (oral 600 mg twice daily) or placebo for 8 days, followed by open-label FTR plus OBR. In the nonrandomized cohort (n = 99), participants with no remaining ARV options were started on open-label FTR (oral 600 mg twice daily) plus OBR on Day 1. The primary endpoint for the randomized cohort was a change in HIV RNA level from baseline at Day 8. In the FTR group, the mean RNA level decrease was 0.79 $\log_{10}$ copies/mL compared to 0.17 $\log_{10}$ copies/mL in the placebo group ($P < 0.001$). At Week 96, 60% of participants in the randomized cohort and 37% of those in the nonrandomized cohort had HIV RNA levels <40 copies/mL, with mean CD4 increases of 205 cells/mm^3 and 119 cells/mm^3, respectively.[79,80] In this study, 15 individuals in the nonrandomized cohort used the CD4 post-attachment inhibitor IBA in combination with FTR and other ARVs. The virological response rate for these participants by snapshot analysis was 53% at Week 48 and 33% at Week 96.
- **Lenacapavir (LEN)** is a LA HIV capsid inhibitor that can be given by one of two initiation schemes (oral plus subcutaneous [SQ] dosing), followed by SQ injections every 6 months (see Appendix B, Table 11 for dosing details).

  A Phase 3 multicenter trial (CAPELLA) enrolled 72 heavily ART-experienced participants who had multidrug-resistant HIV-1 and experienced virologic failure into two cohorts.[81] Cohort 1 (n = 36) included participants who had a <0.5 $\log_{10}$ HIV-1 RNA decline between screening and baseline (i.e., stable viremia at ≥400 copies/mL, confirming lack of response to the failing therapy). The participants were randomized 2:1 to either oral LEN or placebo (on Days 1, 2, and 8) and continued to receive the failing ARV regimen for 14 days to evaluate the virologic effect of LEN functional monotherapy. Starting on Day 15, all participants began on an OBR; those randomized to oral LEN began SQ LEN every 6 months, whereas participants in the placebo arm received oral LEN on Days 15, 16, and 22 followed by SQ LEN on Day 29 (14 days after the first oral LEN dose) and then every 6 months. On Day 15, 88% of participants in the LEN arm and 17% in the placebo arm had HIV RNA level reduction of ≥0.5 $\log_{10}$ copies/mL, with least-squares mean change in HIV RNA level of −2.1 $\log_{10}$ copies/mL versus −0.07 $\log_{10}$ copies/mL for the LEN and placebo arms, respectively ($P < 0.001$). At the end of 26 weeks (i.e., after one dose of SQ LEN), 81% of participants had RNA levels <50 copies/mL, and 89% had RNA levels <200 copies/mL, with a mean change in RNA level of −2.58 ± 1.04 $\log_{10}$ copies/mL.[81] At the end

of 52 weeks (i.e., after two doses of SQ LEN), 83% of participants had RNA levels <50 copies/mL, with 94% of those with at least two active OBR drugs and 67% with no active OBR drugs. The mean CD4 cell count change at 52 weeks[76] was +82 cells/mm^3.

Cohort 2 (n = 36) was a nonrandomized cohort that included participants who either had a ≥0.5 $\log_{10}$ HIV-1 RNA decline from screening to baseline visit or were enrolled after Cohort 1 reached its planned sample size. All participants were started on an OBR and received oral LEN on Days 1, 2, and 8; on Day 15, SQ LEN was started and given every 6 months. After 26 weeks, 83% of the participants had HIV RNA levels <50 copies/mL, and 86% had HIV RNA levels <200 copies/mL. At Week 52, 72% had RNA levels <50 copies/mL, and the mean CD4 cell count change was +113 cells/mm^3.

Oral lead-in therapy was well tolerated overall, with nausea reported in 13% of participants who received LEN. Injection site reactions, which were generally mild and transient, were reported in 63% of the participants.[81]

Twenty-two of 72 (31%) participants met the criteria for resistance testing at confirmed virologic failure through Week 52.[76] LEN-associated capsid resistance mutations were found in 9 of the 22 (41%) participants with confirmed virologic failure. The M66I mutation was the most common mutation, reported in six participants. Four of the nine participants with LEN-associated capsid resistance mutations had no active agent in the OBR. Four others had low plasma concentrations of the OBR drugs at Week 26, suggesting poor adherence of the self-administered OBR, resulting in an unfavorable LEN functional monotherapy.[82]

Taken together, these data[76,82,83] highlight the importance of selecting a robust OBR to support LEN and counseling about adherence to the OBR. Additionally, LEN is a moderate CYP3A4 inhibitor and may increase concentrations of some coadministered drugs, whereas LEN concentration may be significantly decreased in the presence of a strong CYP3A4 inducer (see Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs for further details). Therefore, people with HIV should be routinely counseled to inform all their health care providers of all medications they are taking, including LEN, even though it is not taken daily. Potential drug–drug interactions should be discussed, particularly before a new drug is started, to minimize the risk of toxicities, nonadherence, and drug resistance.

People with HIV who continue to have detectable viremia and who lack sufficient treatment options to construct a fully suppressive regimen also may be candidates for research studies or expanded access programs, or they may qualify for single-person access to an investigational new drug, as specified in the U.S. Food and Drug Administration's Physician Request for a Single Patient Investigational New Drug for Compassionate or Emergency Use. Information about ARV agents that are in clinical studies can be found in the drug database available on the Clinicalinfo website.

People With HIV on ART With Suspected Drug Resistance Who Present With Limited Information (Incomplete or No Self-Reported ARV History, Medical Records, or Drug-Resistance Test Results)

Every effort should be made to obtain the person's ARV history and prior drug-resistance test results; however, this may not always be possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2 to 4 weeks to guide the selection of the next regimen. Another strategy is to start two or three drugs that are predicted to be fully active based on the person's treatment history. If no ARV history is available, a clinician may consider using agents with a high barrier to resistance—such as twice-daily DTG, BIC (which is available only in a combination pill

with FTC/TAF and for which dosage in this setting is unclear), and/or twice-daily boosted DRV—as part of the regimen. Regardless of which strategy is employed, people should be closely monitored for virologic response (e.g., HIV RNA level testing approximately 4 to 8 weeks after reinitiation of therapy), with prompt drug-resistance testing performed if virologic response is inadequate.

People With HIV Who Are Unable to Achieve Viral Suppression Due to Poor Adherence to Oral ART and Who Do Not Have Resistance to Cabotegravir and Rilpivirine

Based on very limited data discussed below, the Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to RPV or CAB, and with shared decision-making between providers and people with HIV **(CIII).**

Some people with HIV cannot reach or maintain viral suppression on oral ART despite intensive adherence support. Although a complete LA injectable regimen may overcome some adherence obstacles for people with viremia, long-term clinical efficacy data are limited in these circumstances and the regimen is only approved for people who are virologically suppressed for at least 3 months. No large, published randomized controlled trial has demonstrated the efficacy of a complete regimen of any INSTI plus NNRTI, including LA CAB/RPV, in people with viremia. However, cohort data are emerging, resulting in two possible approaches to use LA CAB/RPV in this population. If achieving viral suppression with oral ART is possible with intensive adherence support to oral ART, switching to LA CAB/RPV after viral suppression can serve as a goal to incentivize the person to adhere to the oral regimen. Data from the Long-Acting Therapy to Improve Treatment Success in Daily Life (LATITUDE) AIDS Clinical Trial Group (ACTG) A5359 study using this strategy is discussed in Approach #1 below.[84] If achieving viral suppression with oral ART is not possible despite intensive adherence support to oral ART, switching to LA CAB/RPV without viral suppression may be an option in certain circumstances, as discussed in Approach #2 below.

Approach #1: Intensive efforts to achieve viral suppression prior to switching to LA CAB/RPV

Because all of the large LA CAB/RPV studies enrolled participants who were adherent to ART with sustained viral suppression, every effort should be made to achieve viral suppression before considering a switch to LA CAB/RPV, even in people with poor adherence. The Phase 3 prospective, randomized, open-label LATITUDE study was designed to assess this strategy in people who faced challenges with ART adherence. Preliminary data have been presented from this study that enrolled individuals without resistance to CAB or RPV from 33 sites in the United States and Puerto Rico.[84] Participants received adherence support and conditional economic incentives to assist in achieving viral suppression on oral ART. Study participants who experienced viral suppression were randomized to continue oral ART or switch to LA CAB/RPV every 4 weeks. At a planned data safety monitoring board (DSMB) interim efficacy analysis, only 294 (68%) of the 434 participants enrolled achieved viral suppression and were eligible for randomization, with 146 assigned LA CAB/RPV and 148 continuing standard of care (SOC) oral ART. At randomization, it was noted that despite the intensive adherence support, 17% in the LA CAB/RPV arm and 7% in the SOC arm had HIV RNA >200 copies/mL. At Week 48 of the randomized phase, 24% in the LA CAB/RPV arm and 39% in the SOC arm met the primary endpoint of earliest confirmed virologic failure or treatment discontinuation, which did not meet the predefined stringent stopping criteria. However,

two secondary endpoints—virologic failure alone (7% in LA CAB/RPV vs. 25% in SOC) and treatment-related failure (defined as first virologic failure or discontinuation due to adverse events) (10% in LA CAB/RPV vs. 26% in SOC)—met the predefined stopping criteria and were statistically significant. Based upon the totality of the data, in February 2024, the DSMB recommended halting randomization and offering all eligible participants LA CAB/RPV. Of the six participants with virologic failure on LA CAB/RPV, two had new drug-resistance mutations (one conferring high-level resistance to CAB and one conferring high-level resistance to both CAB and RPV). The available data suggest that an intensive effort to achieve viral suppression followed by a switch to LA CAB/RPV may be a viable option for individuals who cannot adhere to an oral ARV regimen. Further analyses and formal publication of LATITUDE study results are pending.

Approach #2: Administer LA CAB/RPV in people with viremia who are unable to achieve viral suppression despite intensive adherence support

Emerging data show that select people with HIV who are unable to achieve viral suppression on an oral ARV regimen despite intensive support might benefit from use of LA CAB/RPV, which is currently not approved for use in this population. Available data with this strategy include an initial case report,[85] followed by outcome data from a compassionate use program,[86] showing that 16 of 28 (57%) people with viremia achieved virologic suppression after a median of 5 months with LA CAB/RPV. Among those with virologic failure and for whom resistance data were available, all had new NNRTI mutations conferring RPV resistance and 50% had new integrase mutations, two of which conferred CAB resistance. Since then, three small observational studies have suggested that LA CAB/RPV may achieve viral suppression in select people with viremia and poor adherence to oral ART.[50-52] In these studies, select people with viremia who were unable to adhere to daily oral ART were initiated on monthly or twice-monthly LA CAB/RPV with or without oral lead-in therapy. At up to 10 months of follow-up, 95% achieved HIV RNA <50 copies/mL. Of those with virologic failure for whom genotypes were available, new reverse transcriptase (e.g., L100I, E138K, Y181I) and/or integrase (e.g., G140S, Q148R, R263K) mutations were detected, conferring intermediate to high resistance to RPV and/or CAB, respectively. Various levels of multidisciplinary support and intensive case management were utilized throughout these studies (e.g., provision of injections in field sites, financial incentives, appointment reminders, and transportation assistance). Despite the intensive support, not all injections were given on time.

In the multisite U.S. Observational Pharmacoepidemiology Research and Analysis (OPERA) cohort,[87] clinical data on the use of LA CAB/RPV were prospectively captured from electronic health records from 84 clinics in 18 U.S. states and territories. Among the 36 individuals who had HIV RNA >200 copies/mL before starting LA CAB/RPV and had at least one follow-up HIV RNA test, 94% had an HIV RNA <200 copies/mL at their last follow-up visit.

Taken together, until additional data are available, these approaches may provide alternatives for individuals with viremia and difficulties with adherence to oral ART, especially for those at the highest risk for disease progression or death. If either of the above approaches are employed, close monitoring is recommended with drug-resistance testing performed if virologic response is inadequate. Importantly, beyond conventional and intensive multidisciplinary team involvement, case management and outreach support are needed to ensure adherence and adequate monitoring while on LA CAB/RPV (see the Adherence to the Continuum of Care section for discussion on strategies to improve adherence in these situations). Caution with close monitoring is advised, as data are unavailable for detailed guidance regarding the need for specific adherence or intensive case management services or whether every 4- or every 8-week LA CAB/RPV will yield similar virologic

outcomes in people with viremia before switching. Every 4-week dosing was used in the LATITUDE study. In the published case series to date in people with viremia, every 4-week dosing was prescribed for most, with the option of switching to every 8 weeks after achieving viral suppression. Until further data are available, it may be prudent to use similar strategies when LA CAB/RPV is being considered. People with HIV and providers need to be aware of the significant risk of developing resistance to NNRTIs, and particularly INSTIs if virologic failure occurs on LA CAB/RPV. Such resistance may limit future treatment options and may also lead to its transmission, which should be balanced with the individual's HIV-related risk for disease progression and death.[88] Closely monitoring for viral responses is advised if LA CAB/RPV is used in people with viremia and who have challenges with adherence.

Summary

The goal of treatment for people with HIV and virologic failure is to establish virologic suppression. The management of people with virologic failure often requires expert advice to construct virologically suppressive regimens. Before modifying a regimen, it is critical to carefully evaluate the potential cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug–drug and drug–food interactions, as well as review HIV RNA and CD4 count changes over time, complete treatment history, and current and previous drug-resistance test results. If HIV RNA suppression is not possible with currently approved agents, consider the use of investigational agents through participation in clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 counts to delay clinical progression.

Table 10. Antiretroviral Options for People With HIV and Virologic Failure

Designing a new regimen for people with HIV who are experiencing treatment failure should always be guided by ARV history and results from current and past resistance testing. This table summarizes the text above and displays the most common or likely clinical scenarios seen in people with virologic failure. For more detailed descriptions, please refer to the texts above and/or consult an expert in HIV drug resistance to assist in the design of a new regimen. It is also crucial to provide continuous adherence support before and after regimen changes.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/– 3TC or FTC (i.e., NNRTI mutations +/– M184V/I).[b] Additional NRTI mutations also may be present.	DTG (or possibly BIC) plus two NRTIs (preferably at least one fully active[c]) **(AI);** *or* Boosted PI plus two NRTIs (preferably at least one fully active) **(AI);** *or* Boosted PI plus INSTI (boosted DRV plus DTG **[AI]**; LPV/r plus RAL **[CI]**)	Resuppression
	Boosted PI plus two NRTIs	Most likely no resistance or resistance only to 3TC or FTC (i.e., M184V/I, without resistance to other NRTIs)[b]	DTG, or possibly BIC, plus two NRTIs (preferably at least one fully active; if only one of the NRTIs is fully active[c] or if adherence is a concern, DTG is currently preferred over other INSTIs) **(AIII);** *or* Continue same regimen **(AII);** *or* Boosted PI plus INSTI (boosted DRV plus DTG **[AIII]**; LPV/r plus RAL **[CI]**); *or* Another boosted PI plus two NRTIs (at least one fully active[c]) **(AIII).**	Resuppression
	INSTI plus two NRTIs	If failure with no INSTI resistance	Boosted PI plus two NRTIs (preferably at least one fully active[c]) **(AIII);** *or* DTG, or likely BIC, plus two NRTIs (preferably at least one fully active[c]) **(AIII);** *or* DRV/r plus DTG **(AIII)**	Resuppression
		If failure on EVG or RAL, often have INSTI resistance, but potentially susceptible to DTG	Boosted PI plus two NRTIs (preferably at least one fully active[c]) **(AIII);** *or*	Resuppression

Table 10. Antiretroviral Options for People with HIV and Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
		Can have 3TC or FTC resistance.	DTG[d] twice daily or possibly BIC (if HIV is sensitive) plus two fully active NRTIs **(BIII);** *or* DTG[d] twice daily or possibly BIC (if HIV is sensitive) plus a boosted PI (preferably DRV/r) **(AIII).**	
	INSTI plus NNRTI (DTG/RPV or LA CAB/RPV)	INSTI and/or NNRTI resistance possible	Use ART history and past and current resistance testing to design a new regimen. Consult an expert in drug resistance as needed.	Resuppression
Second Regimen Failure and Beyond	Drug resistance with fully active treatment options—	Use past and current genotypic- +/– phenotypic-resistance testing and ART history when designing new regimen.	New regimen according to original treatment type—	Resuppression
	(i) Boosted PI, but not second-generation INSTI, fully active		(i) Boosted PI with two NRTIs (preferably at least one fully active)	
	(ii) Second-generation INSTI, but not boosted PI, fully active		(ii) DTG or BIC with two NRTIs (preferably at least one fully active)	
	(iii) Both PI and INSTI fully active		(iii) The two options above or boosted PI with INSTI	
	Multiple or extensive drug resistance with few treatment options (e.g., fully active boosted PI or second-generation INSTI unavailable)	Use past and current genotypic- and phenotypic-resistance testing to guide therapy. Confirm with a viral tropism assay when use of MVC is considered. Consult an expert in drug resistance if needed.	New regimen should include at least two, and preferably three, fully active agents, including those with novel mechanisms of action (e.g., IBA, FTR, LEN). If fewer than three fully active drugs, include as many fully active drugs as possible, along with potentially partially active drugs **(BII).** Consider enrollment into clinical trials or expanded access programs for investigational agents if available. Discontinuation of all ARV drugs **is not recommended (AI).**	Resuppression if possible; otherwise, keep viral RNA levels as low as possible and CD4 count as high as possible.

Table 10. Antiretroviral Options for People with HIV and Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
People With Suspected Drug Resistance and Limited or Incomplete ARV and Resistance History	Unknown	Obtain medical records if possible. Resistance testing may be helpful in identifying drug-resistance mutations, even if the person has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.	Consider restarting the old regimen with careful monitoring of virologic response and early resistance testing if inadequate virologic suppression. If no ARV history is available, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG, BIC, and/or boosted DRV) with careful monitoring of virologic response and early resistance testing, if inadequate virologic suppression.	Resuppression

[a] When switching an ARV regimen in a person with HBV/HIV coinfection, ARV drugs that are active against HBV and have a high resistance barrier to HBV (i.e., tenofovir) should be continued as part of the new regimen, or another HBV drug (i.e., entecavir) should be started. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

[b] If other NRTI-resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

[c] See text for details and additional options in special settings.

[d] Response to DTG depends on the type and number of INSTI mutations.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir

Isolated Central Nervous System Virologic Failure and Neurologic Symptoms

Cerebrospinal Fluid Viral Escape

Presentation with new-onset central nervous system (CNS) signs and symptoms has been reported as a rare form of "compartmentalized" virologic failure. People experiencing this present with new, usually subacute, neurological symptoms that are associated with a breakthrough of HIV replication within the CNS compartment, despite relative plasma HIV RNA suppression. In this case, cerebrospinal fluid (CSF) HIV RNA shows higher concentrations than in plasma.[89-91] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging (MRI) and abnormal CSF findings with characteristic lymphocytic pleocytosis.[92] In most (though not all) people, drug-resistant CSF virus is evident.[93] Consensus among experts is that this "neurosymptomatic" form of CNS viral escape should be treated through optimization of ARV regimens based on drug-resistance testing results if available **(CIII).**[94] Although drug-resistance testing of HIV in CSF can be used to guide changes in the ARV regimen, according to the principles outlined above for plasma HIV RNA resistance, such testing typically needs to be conducted in a research setting. If CSF HIV drug-resistance testing is not available, the regimen may be changed based on the person's treatment history or on predicted drug penetration into the CNS **(CIII).**[95-98]

This "neurosymptomatic" CNS viral escape should be distinguished from "neuroasymptomatic" escape, defined as—

- The incidental detection of asymptomatic and mild CSF HIV RNA elevation, which is similar to plasma viral blips in that it is usually transient with low levels of CSF HIV RNA and has been associated with PI-based regimens[99-101]; *or*
- A transient increase in CSF HIV RNA that is related to other CNS infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster).[102]

There is not clear evidence to support a change in an ARV regimen for incidentally detected "neuroasymptomatic" escape, although careful clinical review and follow-up of each person with this condition are recommended to monitor for the emergence of neurologic symptoms or systemic viremia.[94] There does not appear to be an association between these asymptomatic CSF HIV RNA elevations and the relatively common chronic, usually mild, neurocognitive impairment in people with HIV who show no evidence of CNS viral breakthrough.[103]

Neurological Symptoms in People With HIV on Antiretroviral Therapy

Evidence is currently not available to support empiric intensification or switch of ARV regimens in people on systemically suppressive ART with mild neurological and/or cognitive symptoms who do not have documented CSF escape. Such individuals should be referred for neurological evaluation to determine if further evaluation is indicated. This may include blood laboratory testing, lumbar puncture, neuropsychological testing, and MRI to evaluate for CSF escape, as well as other causes of neurological symptoms. A recent multinational randomized, double-blinded, placebo-controlled trial randomized 191 ART-experienced participants—with cognitive impairment and suppressed plasma HIV RNA level and not taking an INSTI—to one of three arms: dual placebo, addition of DTG plus placebo, or DTG plus MVC. Compared with placebo, ART intensification with DTG or DTG plus MVC did not alter neuropsychological performance or depressive symptoms over time in participants with cognitive impairment.[104]

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Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression

Updated: May 26, 2021
Reviewed: May 26, 2021

Key Considerations and Recommendations
• Persistently low CD4 T lymphocyte (CD4) cell counts and immune activation are each associated with increased AIDS- and non-AIDS-related morbidity and mortality among individuals with antiretroviral therapy (ART)-mediated viral suppression. • Adding antiretroviral (ARV) drugs to a suppressive ARV regimen (ART intensification) does not improve CD4 cell recovery or reduce immune activation and, therefore, **is not recommended (AI).** • In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce all relevant markers of immune activation and **is not recommended (BIII).** • Interleukin-2 **is not recommended (AI)** to increase CD4 cell counts and/or decrease immune activation, because clinical trial data demonstrated no clinical benefit. • Other interventions designed to increase CD4 cell counts and/or decrease immune activation **are not recommended** outside of a clinical trial, because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression **(AII).** • Efforts to decrease morbidity and mortality during ART-mediated viral suppression should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and regular exercise; treating hypertension and hyperlipidemia). • Monitoring markers of immune activation and inflammation is not recommended, because no intervention targeting immune pathways has proven to improve the health of individuals with HIV, and many blood markers that predict morbidity and mortality fluctuate within individuals **(AII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Despite marked improvements in antiretroviral treatment (ART), morbidity and mortality in individuals with HIV continue to be greater than in the general population, particularly when ART is delayed until advanced disease stages. These morbidities include cardiovascular disease, many non-AIDS cancers, non-AIDS infections, chronic obstructive pulmonary disease, osteoporosis, type 2 diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and the frailty phenotype.[1] Although health-related behaviors and toxicities of antiretroviral (ARV) drugs are important factors, immune characteristics, such as a poor CD4 T lymphocyte (CD4) cell recovery and persistent immune activation and inflammation, likely also contribute to the disease risk among persons with HIV.

Poor CD4 Cell Recovery

As long as ART-mediated viral suppression is maintained, peripheral blood CD4 cell counts in most individuals with HIV will continue to increase for at least a decade. The rate of CD4 cell recovery is typically most rapid in the first 3 months of suppressive ART, followed by more gradual increases over time.[2-4] If ART-mediated viral suppression is maintained, most individuals will eventually recover CD4 counts in the normal range (>500 cells/mm^3); however, approximately 15% to 20% of individuals who initiate ART at very low CD4 counts (<200 cells/mm^3) may plateau at abnormally

low CD4 cell counts.[3-5] Early initiation of ART in individuals with recent HIV diagnoses likely provides the best opportunity for maximal CD4 cell recovery.[6]

Persistently low CD4 cell counts despite ART-mediated viral suppression are associated with increased risk of morbidity and mortality. For example, individuals with HIV who have CD4 counts <200 cells/mm^3, despite at least 3 years of suppressive ART, had a 2.6-fold greater risk of mortality than those with higher CD4 cell counts.[7] Lower CD4 cell counts during ART-mediated viral suppression are associated with an increased risk of non-AIDS morbidity and mortality,[8-11] including cardiovascular disease,[12] osteoporosis and fractures,[13] liver disease,[14] and infection-related cancers.[15] The prognostic importance of higher CD4 cell counts likely spans all ranges of CD4 cell counts, though incremental benefits are harder to discern once CD4 counts increase[16] to >500 cells/mm^3.

Individuals with poor CD4 cell recovery should be evaluated for modifiable causes of CD4 cell lymphopenia. Concomitant medications should be reviewed, with a focus on those known to decrease white blood cells or, specifically, CD4 cells. If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., hepatitis C virus, HIV-2) and serious medical conditions (e.g., malignancy) also should be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and in those with CD4 counts consistently below 100 cells/mm^3.

In rare cases, CD4 cell counts actually decline, despite suppressive ART in the absence of an obvious clinical cause. Severe derangements in interleukin (IL)-7-**mediated** naive T cell homeostasis have been reported in these individuals, although the pathophysiology is likely to be multifactorial.[17-19]

Despite strong evidence linking low CD4 cell counts and increased morbidity during ART-mediated viral suppression, no adjunctive therapies that increase CD4 cell count beyond levels achievable with ART alone have been proven to decrease morbidity or mortality. Adding ARV drugs to an already suppressive ARV regimen does not improve CD4 cell recovery,[20-25] and does not reduce morbidity or mortality. Therefore, ART intensification is not recommended as a strategy to improve CD4 cell recovery **(AI).** Similarly, for individuals who are already maintaining viral suppression, switching ARV drug classes also does not consistently improve CD4 cell recovery and is not recommended **(BIII).**[26]

Immune-based therapies also have been investigated as a strategy to increase CD4 cell counts (e.g., IL-2, IL-7, growth hormone). Two large clinical outcome trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2 for improving CD4 cell recovery. IL-2 adjunctive therapy resulted in substantial CD4 cell count increases but with no observable clinical benefit.[27] Therefore, IL-2 is **not recommended (AI).** Given the lack of established clinical benefit to date, other immune-based therapies should not be used except in the context of a clinical trial.

Persistent Immune Activation and Inflammation

HIV infection results in heightened systemic immune activation and inflammation, which predict more rapid CD4 cell decline and progression to AIDS and death, independent of plasma HIV RNA levels.[28] Although immune activation declines with suppressive ART, it often persists at abnormal levels in many individuals with HIV maintaining long-term ART-mediated viral suppression—even in those with CD4 cell recovery to normal levels.[29, 30] Immune activation and inflammatory markers (e.g., IL-6, D-dimer, high sensitivity C-reactive protein (hs-CRP) also predict mortality and non-

AIDS morbidity during ART-mediated viral suppression, including cardiovascular and thromboembolic events, cancer, neurocognitive dysfunction, and frailty.[28] A low CD4/CD8 ratio also might reflect this inflammatory state to some degree,[31] although it predicts AIDS events far more strongly than non-AIDS morbidity.[32] Although individuals with poor CD4 cell recovery (i.e., counts persistently <350 cells/mm^3) tend to have greater immune activation and inflammation than those with greater recovery,[29] the relationship between innate immune activation and inflammation and morbidity/mortality is largely independent of CD4 cell count.[33, 34] Even in individuals with CD4 counts >500 cells/mm^3, immune activation and inflammation are associated with increased morbidity and mortality.[35, 36]

ART as a Strategy to Reduce Inflammation

Early diagnosis and treatment of HIV is, potentially, an effective strategy to achieve a lower level of persistent immune activation with ART. Most inflammatory markers decline during the first several months of ART and achieve a stable "setpoint" within 1 to 2 years.[37, 38] In observational studies, people with HIV who initiated ART during acute HIV infection appeared to achieve a lower immune activation setpoint during ART-mediated viral suppression than those who started ART at later disease stages.[39, 40] Indeed, those randomized to the immediate treatment arm of the START trial appeared to achieve a lower early inflammatory setpoint than those who were randomized to delayed therapy.[41] Longer-term follow-up of START participants is needed to determine whether such a reduced inflammatory setpoint persists and translates into reduced morbidity and mortality. Collectively, these data reinforce the recommendation to start ART as soon as possible after HIV diagnosis (see Initiation of Antiretroviral Therapy).

Although earlier initiation of ART appears to consistently reduce the inflammatory setpoint during ART, intensifying or modifying ART after viral suppression is already achieved does not appear to consistently reduce immune activation. For example, adding ARV drugs to an already suppressive ARV regimen (or ART intensification) does not consistently improve immune activation.[20-23, 25] Although some studies have suggested that switching an ARV regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation,[42-44] these studies have limitations and results are not consistent across markers and among studies. Thus, at this time, ART modification cannot be recommended as a strategy to reduce immune activation **(BIII).**

Other Immune-Based Strategies

Because persistent immune activation is associated with morbidity and mortality among people with HIV who are virologically suppressed with ART, strategies targeting immune-mediators of inflammation are under investigation. Although the efficacy of canakimumab is not yet proven in people with HIV, the CANTOS trial provided important proof of concept for the causal role of inflammation in the risk of multi-morbidity in people without HIV but with cardiovascular disease. The study demonstrated that treatment with canakimumab, a human monoclonal antibody targeting cytokine IL-1β, a driver of the IL-6 signaling pathway, reduced cardiovascular events and cancer death.[45] In people with HIV, canakinumab and the IL-6 inhibitor tocilizumab have been shown to reduce blood levels of markers of inflammation and immune activation.[46, 47] Nevertheless, it remains unclear whether the potential risks of these therapies, such as the increased risk of death from sepsis observed in the CANTOS trial, might outweigh any benefits in people with HIV. Therefore, interventions targeting immune mediators of inflammation are not currently recommended for clinical use for the treatment of immune activation in people with HIV **(AII).**

Treatments Targeting Traditional Risk Factors and Inflammation

Beyond the well-established clinical benefit for reducing cardiovascular events, HMG-CoA reductase inhibitors (or statins) have been shown to improve biomarker levels of inflammation (e.g., hsCRP) and immune activation in the general population.[48-50] This premise, and the data suggesting similar benefit among people with HIV, motivated the design of a large clinical trial (REPRIEVE), now fully enrolled, to determine whether pitavastatin reduces cardiovascular events in people with HIV who do not already have a clinical indication for cholesterol-lowering therapy. [51] Although the results will not be known for several years, in addition to identifying the primary cardiovascular outcomes, assessing the impact of pivitastatin on non-cardiovascular events (such as cancer, osteoporotic fractures, and frailty phenotypes) that may be linked to the inflammatory state also will be valuable. Similarly, it remains unclear whether statins might further increase type 2 diabetes risk, which is increased in people with HIV.[52] Other commonly used medications with anti-inflammatory properties—like aspirin, angiotensin-converting enzyme inhibitors, methotrexate, and angiotensin receptor blockers[53]—have failed to consistently reduce biomarkers of immune activation and/or inflammation in people with HIV in randomized controlled trials and,[54-57] as a result, clinical outcome trials specific to this population are not anticipated.

Treatments Targeting Putative Drivers of the Inflammatory State

Other investigational approaches to reduce the inflammatory state in patients with viral suppression on ART have focused on the presumed root drivers of inflammation, including HIV reactivation from latently infected cells, microbial translocation, and chronic co-infections, particularly cytomegalovirus (CMV).[28] Thus far, the only approach targeting these root drivers that has broadly reduced systemic immune activation is treating asymptomatic CMV co-infection,[58] an approach that is being pursued further in a prospective larger trial (ACTG A5383). Presently, none of these strategies have been proven to be effective in clinical endpoint trials, so these interventions should be pursued only in the context of clinical trials.

Monitoring Inflammation

In the absence of proven interventions, there is no clear rationale to routinely monitor levels of immune activation and inflammation in treated HIV infection. Furthermore, many of the inflammatory markers that predict morbidity and mortality fluctuate significantly in individuals with HIV. Thus, clinical monitoring with immune activation or inflammatory markers **is not currently recommended (AII).** The focus of care to reduce chronic non-AIDS morbidity and mortality should be on maintaining ART-mediated viral suppression and addressing strategies to reduce risk factors (e.g., smoking cessation, healthy diet, and exercise) and managing chronic comorbidities, such as hypertension, hyperlipidemia, and diabetes **(AII).**

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Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

Updated: September 12, 2024
Reviewed: September 12, 2024

Key Considerations and Recommendations
• Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance have made it possible to consider switching a person with HIV from an effective ARV regimen to an alternative ARV regimen in some situations.
• The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options.
• Adverse events, drug–drug or drug–food interactions, pill burden, pregnancy, cost, stigma, inconvenience from taking oral medications, or the desire to simplify a regimen may prompt regimen optimization.
• It is critical to review a person's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results before selecting a new ARV regimen **(AI).**
• People with HIV who have no history of drug-resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in people who are ARV-naive **(AI)** or to NRTI-sparing options extensively researched in switch studies, such as dolutegravir (DTG) plus rilpivirine (RPV) **(AI)** or long-acting cabotegravir plus rilpivirine (LA CAB/RPV) **(AI).**
• For regimen optimization in the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, if an NRTI is to be included in the new regimen, two NRTIs (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF] plus emtricitabine [FTC] or lamivudine [3TC]) should be included, along with a fully active drug with a high resistance barrier, such as DTG **(AII),** bictegravir (BIC) **(BIII),** or boosted darunavir **(BIII).** Alternatively, as noted above, an NRTI-sparing regimen (such as DTG/RPV **[AI]** or LA CAB/RPV **[AI]**) is possible if there is no evidence of prior integrase strand transfer inhibitor (INSTI) or RPV resistance.
• Monotherapy with either a boosted protease inhibitor or an INSTI has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy **is not recommended (AI).**
• When switching an ARV regimen in a person with chronic hepatitis B virus (HBV)/HIV coinfection, HBV-active drugs that are potent and have a high barrier to resistance (i.e., TAF, TDF, or entecavir) should be used **(AII).** Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.
• Consultation with an HIV specialist is recommended when planning a regimen switch for a person with a history of resistance to two or more drug classes **(AIII).**
• Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

With currently available antiretroviral therapy (ART), most people with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in antiretroviral (ARV) treatment and a better understanding of drug resistance have made it possible to consider switching a person with HIV from one effective regimen to another in some situations. When considering optimization—a switch in therapy to improve certain aspects of therapy—clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Table 20 and Table 21 in the Adverse Effects of Antiretroviral Agents section for a more in-depth discussion of toxicities)
- To prevent or mitigate drug–drug interactions (see Drug–Drug Interactions)
- To eliminate food requirements
- To switch to a long-acting (LA) injectable regimen for convenience, to relieve pill fatigue, or to decrease potential stigma or disclosure concerns associated with taking daily oral medications
- To allow optimal use of ART during pregnancy or when pregnancy is desired or may occur (see Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Optimization

Maintain Viral Suppression

The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance mutations, the person may require a more complex and/or a less tolerated regimen.

Careful Review of Antiretroviral Treatment and Drug-Resistance History Before Optimization

Before switching treatments, it is critical to thoroughly assess a person's full ARV history, including virologic responses, inferred resistance (as discussed below), cumulative resistance test results, and any past ARV-related intolerances, toxicities, or adverse reactions **(AI).**

If a person with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can safely assume that no new drug-resistance mutations emerged while the person was on the suppressive regimen. In people with a history of virologic failure or pre-treatment drug resistance, a review of cumulative resistance test results and clinical and virologic response to prior regimens is essential when designing a new regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype (if available), phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a drug-resistance mutation—even when it is not detected in the person's most recent drug-resistance test—can be archived in the HIV reservoir and reemerge under the appropriate selective drug pressure. Resistance often can be inferred from the ARV history. For people with documented failure on a regimen that includes drugs with relatively low barriers to resistance—such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC)—a clinician should assume that there is resistance to these drugs, so-called *inferred resistance*. When uncertain about prior resistance, it is generally not advisable to switch from a suppressive ARV regimen, unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a

relatively high barrier to resistance—such as those that include pharmacologically boosted protease inhibitors (PIs), dolutegravir (DTG), or bictegravir (BIC)—to one with a lower barrier to resistance.[1] The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that clinicians consult an HIV specialist when contemplating optimization for a person with a history of resistance to two or more drug classes **(AIII).**

If optimization is considered in people with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For those who have no prior virologic failures and who are on their first or second regimen, or who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide valuable information. In individuals with a history of multiple prior failures or multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. However, whenever proviral DNA genotypic testing is used, the results must be interpreted with caution because these assays may not detect any or all drug-resistance mutations, especially those that were selected by a previous ARV regimen.[2] In addition, these assays may identify mutations that appear inconsistent with a person's response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see Drug-Resistance Testing).

For People With HBV/HIV Coinfection

When switching an ARV regimen in a person with active hepatitis B virus (HBV)/HIV coinfection (hepatitis B surface antigen [HBsAg] positive), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) (generally given with 3TC or FTC) should be continued as part of the new regimen. Both TDF and TAF are active against HBV and can be used as HBV monotherapy. Although 3TC and FTC are active against HBV, their use as monotherapy against HBV infection **is not recommended (AII)** because emergent HBV resistance to these drugs is highly likely. If TAF or TDF cannot be used, entecavir—a potent antiviral with a high HBV resistance barrier—should be used to treat HBV alongside a fully suppressive ARV regimen **(AII).** Entecavir should not be used without an active ARV regimen to prevent the development of the HIV M184V resistance mutation. Discontinuation of HBV antivirals may lead to reactivation of HBV, which can result in serious hepatocellular damage and death. Refer to the Hepatitis B Virus/HIV Coinfection section for specific recommendations.

Screening for HBV for People With No History of HBV/HIV Coinfection

People with HIV and unknown or nonimmune HBV status should be screened for HBV infection before switching an ARV regimen to one that does not include TAF or TDF plus 3TC or FTC (e.g., DTG/rilpivirine [RPV], DTG/3TC, LA cabotegravir [CAB]/RPV). If a person with HIV shows no evidence of chronic HBV infection (i.e., negative for hepatitis B surface antibody [HBsAg]) and is not immune to HBV (i.e., negative for HBsAb), vaccination should be initiated while considering the ARV switch (including in those with isolated hepatitis B core antibody [HBcAb]).

People with HIV and prior exposure to HBV infection without evidence of chronic infection (i.e., negative HBsAg, positive HBcAb, and either positive or negative HBsAb) are likely at low risk (<1%) of HBV reactivation and even lower risk of HBV reactivation-associated hepatitis, despite the discontinuation of NRTIs. However, there are no published studies to confidently estimate risk in this population. Within this group, those with positive HBsAb are at the lowest risk for HBV reactivation, although HBV reactivation has been described when HBV active therapy is withdrawn as part of an

ART regimen in this situation.[3] See more information in the Hepatitis B Virus Infection section in the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV.

For people previously exposed to HBV, alanine aminotransferase (ALT) should be monitored for 6 months (e.g., at the time of HIV viral load follow-up visits) after switching from ART that includes tenofovir (TDF or TAF) to one that does not include either of these drugs. An increase in ALT levels should prompt HBV DNA testing to assess for the reactivation of HBV. The presence of HBV reactivation would require the immediate addition of TAF, TDF, or entecavir to the ARV regimen.

Assessment for Potential Drug Interactions

Before switching a regimen, it is important to review each ARV drug in the new regimen and concomitant medications to assess whether any potential drug–drug interactions exist. For example, oral rilpivirine (RPV) and atazanavir (ATV) interact with acid-lowering agents, and many ARV drugs may interact with drug transporters or drugs that are inhibitors, inducers, or substrates of cytochrome P450 (CYP) enzymes (see Drug–Drug Interactions). In addition to new drug interactions, the discontinuation of some ARV drugs also may necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications, which may have been previously managed with dose adjustments, will need to be reevaluated in the context of the new ARV regimen.

Assessment for Pregnancy or Pregnancy Potential

People of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant or desires pregnancy, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use at the time of conception or during pregnancy. All pregnancies that occur while an individual is receiving ART should be reported to the Antiretroviral Pregnancy Registry.

Monitoring After Switching Antiretroviral Therapy

After a treatment switch, people with HIV should be evaluated closely for 3 months (e.g., a clinic visit or telephone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 12 weeks after the switch) **(AIII).** The purpose of this close monitoring is to ensure the person clearly understands their prescribed ART regimen, assess medication tolerance, and conduct targeted laboratory testing when there are preexisting laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormality prompted the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the ART change. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound over the first 2 to 3 months, clinical and laboratory monitoring may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

Specific Regimen Optimization Considerations

As with the recommendation for people who are starting ART, the use of a 2- or 3-drug ARV regimen (as discussed below) is generally recommended when switching ART in people with suppressed viral loads **(AI).** People who have no history of resistance mutations or virologic failure

can likely switch to any regimen that has been shown to be highly effective in people who have not been on ART **(AI).** People with prior drug resistance can be switched to a new regimen based on their ARV history and cumulative resistance testing results. Monotherapy with either a boosted PI or an integrase strand transfer inhibitor (INSTI) has been explored in several trials or cohort studies.[4-7] Both INSTI[8] and boosted PI[9] monotherapy have been associated with higher rates of virologic failure than combination regimens. In addition, INSTI monotherapy has been associated with the development of resistance;[10,11] therefore, ARV monotherapy as a maintenance strategy is **not recommended (AI).**

Optimization Strategies With Good Supporting Evidence for People Without Known Drug Resistance

Many clinical trials have enrolled participants with stable, suppressed viral loads without known underlying drug resistance and switched them to another regimen. Most of these studies demonstrated maintenance of viral suppression, some of which are referenced below. However, some regimen switches have had limited success in clinical trials but have informed optimization strategies. The SWITCHMRK 1 and 2 studies illustrated the importance of considering the possibility of underlying drug resistance before switching therapy in those with virologic suppression, particularly when the switch is to a drug with a low barrier to resistance.[1] In the two SWITCHMRK studies, those with viral suppression on two NRTIs plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies found that individuals with a history of previous virologic failure had a higher risk of failure after switching to the RAL-based regimen. This finding is likely explained by underlying NRTI resistance, a setting where viral suppression can generally be maintained by drugs with a high barrier to resistance, such as boosted PIs, but is less likely to maintain viral suppression when switched to a drug with a low barrier to resistance, such as RAL. The strategies listed below support these observations and principles of optimizing therapy and include a discussion about switching ART regimens in those with underlying resistance.

Three-Drug Regimens

Within-Class Switches

Within-class switches (e.g., switching from one INSTI to another INSTI) may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, lower pill burden, or do not require PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. Below are examples of within-class switch strategies that are proven to be effective in clinical trials or are likely to be effective in those without underlying drug resistance:

- From TDF[12,13] or abacavir (ABC)[14] to TAF
- From RAL or elvitegravir/cobicistat (EVC/c)[15] to BIC or DTG
- From DTG[16-18] to BIC or BIC to DTG
- From efavirenz to RPV,[13,19] doravirine (DOR),[20] or RPV to DOR

Between-Class Switches

Between-class switches (e.g., switching from a boosted PI to an INSTI) generally maintain viral suppression, provided there is no resistance to the other components of the regimen. In general, such switches should be avoided if any doubt exists about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch. The following are examples of between-class switches that have been proven to be effective in clinical trials or are likely to be effective in those without underlying drug resistance:

- From a boosted PI to a second-generation INSTI (e.g., DTG,[21] BIC[22])
- From a boosted PI to RPV[23] or DOR[20]
- From an NNRTI to a second-generation INSTI[24,25] or a boosted PI

Two-Drug Regimens

Some two-drug ARV regimens are effective in maintaining HIV virologic control in people who initiated therapy with three-drug regimens and achieved sustained virologic suppression for at least 3 months. However, none of the two-drug regimens are effective as treatment for HBV and are therefore not recommended for people with HBV coinfection. In people with HBV who cannot take TAF or TDF, these regimens can be considered if used with a potent, high barrier-to-resistance anti-HBV active medication (i.e., entecavir) **(AII).** See the section above on HBV considerations during optimization. The following are examples of successful strategies studied in clinical trials for switching from 3- to 2-drug regimens in people with suppressed HIV.

Dolutegravir Plus Rilpivirine

Two Phase 3 trials, SWORD-1 and SWORD-2, demonstrated noninferior efficacy of switching to a 2-drug regimen of DTG with RPV compared to continuing a first or second ARV regimen in individuals with suppressed HIV-RNA without prior virologic failure.[26] Individuals were excluded from the study if they had active HBV infection (unless the person was also on a specific HBV active regimen), resistance to DTG or RPV, or significant drug interactions. DTG/RPV is suitable for use in people with an isolated K103N resistance mutation and in those with NRTI resistance. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir).

Dolutegravir Plus Lamivudine or Emtricitabine

A switch from a stable 3-drug ARV regimen to DTG plus 3TC or FTC as a maintenance strategy in people with ongoing virologic suppression and no history of prior virologic failure or resistance to these agents was noninferior to continuing a 3-drug therapy in a large randomized clinical trial (TANGO),[27] in smaller clinical trials,[28-30] and in observational studies[31-33] **(AI).** Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir). 3TC or FTC monotherapy is not considered standard of care for HBV treatment because of a high risk of emerging resistance.[34]

Boosted Protease Inhibitor Plus Lamivudine

A boosted PI plus 3TC is a reasonable 2-drug optimization option in individuals without resistance who are suppressed on a current regimen and who do not have active HBV infection. Pill burden and potential drug interactions are limitations compared to the above 2-drug regimens. Several regimens using a boosted PI plus 3TC have been shown to be effective in clinical trials, including darunavir/ritonavir (DRV/r) **(BI),**[35] darunavir/cobicistat (DRV/c) **(BIII),** atazanavir/ritonavir (ATV/r) **(CI),**[36,37] and LPV/r **(CI).**[38] Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir). 3TC or FTC monotherapy is not considered the standard of care for HBV treatment because of a high risk of emerging resistance.[34]

Boosted Darunavir Plus Dolutegravir

An open-label, Phase 3b, noninferiority clinical trial evaluated the continuation of DRV/r plus two NRTIs versus a switch to DRV/r plus DTG; the switched regimen was noninferior.[39] Because of the small sample size of this study, the regimen of DRV/r plus DTG is recommended only in the absence of other alternative options but can be considered in particular for individuals with resistance and/or intolerance to 3TC (or FTC), ABC, and TDF (or TAF) **(CI).** Similar results were observed in two small observational studies.[40,41] Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (i.e., TAF, TDF, or entecavir).

Long-Acting Intramuscular Cabotegravir Plus Rilpivirine

Long-acting ARV medications provide the convenience of reduced dosing frequency and may improve quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or stigma associated with daily oral medication. Long-acting (LA) intramuscular (IM) injectable formulations of the INSTI cabotegravir (CAB) and the NNRTI RPV are approved by the U.S. Food and Drug Administration (FDA) to be given once monthly or every 2 months as a complete regimen for individuals ≥12 years old with sustained (e.g., ≥3 months) virologic suppression (HIV-1 RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and with no known or suspected resistance to either CAB or RPV.[42-44]

Panel's Recommendation

The Panel recommends that monthly or every 2-month LA CAB/RPV can be used to replace an existing oral ARV regimen in people with HIV who fulfill all of the following criteria **(AI)**:

- Sustained viral suppression for at least 3 months
- No history of documented or suspected resistance to either CAB or RPV
- No active HBV infection (unless also receiving TAF, TDF, or entecavir)
- Not pregnant or actively planning pregnancy
- Not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV (see Tables 24b and Table 24d)

Oral lead-in therapy with CAB and RPV is optional and can be done based on provider–patient discussion.

Clinical Trial Data

Two Phase 3 clinical trials (ATLAS and FLAIR) randomized almost 1,200 participants with HIV-1 and viral suppression on oral ART to receive once-monthly LA CAB/RPV or to continue their oral ARV regimens.[45,46] Participants could not have prior resistance to INSTIs or NNRTIs (except the K103N mutation), previous virologic failure (ATLAS trial), or active or occult HBV infection. Both studies used a 1-month oral lead-in of once-daily CAB 30 mg with RPV followed by injectable LA CAB/RPV monthly (loading dose x 1 followed by maintenance dosing). In the intention to treat the exposed population, HIV RNA >50 copies/mL at Week 48 occurred in 11 (1.9%) participants in the IM arms and 10 (1.7%) participants in the oral therapy arms (combining data from both studies) demonstrating that long-acting therapy was noninferior to continued oral therapy.[47] Virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common.

The ATLAS-2M study compared LA CAB 600 mg/RPV 900 mg every 8 weeks (n = 522) versus LA CAB 400 mg/RPV 600 mg every 4 weeks (n = 523) in ART-experienced adults.[48] At 48 and 96 weeks, every 8-week dosing was noninferior to every 4-week dosing (HIV RNA ≥50 copies/mL; 2% vs. 1% at 48 weeks).[49,50]

In the SOLAR study, 687 individuals who were virologically suppressed on BIC/FTC/TAF were randomized 2:1 to either switch to LA CAB/RPV every 2 months or remain on BIC/FTC/TAF.[51] At 48 weeks LA CAB/RPV was virologically noninferior to continued BIC/FTC/TAF with 1% versus <1% virologic failure, respectively. There was also no difference in viral suppression with or without oral lead-in when initiating LA CAB/RPV therapy. Based on these data and other existing data, oral lead-in therapy is now considered optional (see the CABENUVA FDA drug label).

Lastly, the Cabotegravir and Rilpivirine Efficacy and Safety (CARES) trial, an open-label trial conducted in Africa, randomized people with HIV and viral suppression to receive LA CAB/RPV every 8 weeks or to continue with their oral ARV regimen. At 48 weeks, 246 of 255 (96%) in the LA CAB/RPV arm and 250 of 257 (97%) in the oral ARV arm maintained HIV RNA <50 copies/mL. Two LA CAB/RPV participants had virologic failure at Week 48 and developed high-level resistance to both CAB and RPV.[52]

Adverse Effects

The most common adverse events associated with LA CAB/RPV are injection site reactions (ISRs) which occurred in more than 80% of participants at least once. ISRs reduce in frequency over time, occurring in about 10% to 30% of participants after the first year. ISRs were generally mild to moderate, with 99% being Grade 1 or 2 and the median duration of symptoms being 3 days. Hypersensitivity reactions, post-injection reactions, hepatotoxicity, and depressive disorders have also been reported.[49,53]

Practical Considerations When Using Long-Acting Injectable Cabotegravir and Rilpivirine

When prescribing LA CAB/RPV, clinicians should refer to the FDA product label[42] for guidance with the following practical considerations:

- Injection techniques, including injection sites and needle length in people with body mass index >30 kg/m^2

- Several drugs, particularly those interacting with CYP3A or uridine diphosphate glucuronosyltransferase 1A1, are contraindicated with CAB and RPV (oral and/or IM) due to significant drug interactions (Drug–Drug Interaction Tables 24b and 24d).
- Management strategies for missed doses of IM injections and use of oral bridging therapy

HIV Viral Load and Drug-Resistance Testing Monitoring

HIV viral load monitoring should be performed 4 to 8 weeks after a switch to LA CAB/RPV. HIV viral load also should be checked in people with unplanned missed visits and delayed dosing of LA CAB/RPV. When viremia develops during LA therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in people with missed doses should not be delayed while awaiting viral load and resistance test results. In a pooled analysis from FLAIR, ATLAS, and ATLAS-2M, confirmed virologic failure was more common in the setting of baseline, proviral, RPV resistance-associated mutations; HIV-1 subtype A6 (rare in the United States); higher baseline body mass index; and lower week-8 trough RPV concentration.[54] However, some recent studies did not observe worse outcomes in people with a high body mass index (Opera Cohort and CARES Study).[55,56] In the setting of confirmed virologic failure on LA CAB/RPV, resistance to NNRTIs and INSTIs is common.[57-59]

Pregnancy Considerations

Initiation of LA CAB/RPV is not recommended during pregnancy. Clinicians should refer to the Perinatal Guidelines for recommendations in managing people who become pregnant or are planning pregnancy while receiving LA CAB/RPV. Health care providers are strongly encouraged to register people with HIV who become pregnant while receiving LA CAB/RPV in the Antiretroviral Pregnancy Registry.

Considerations Regarding Long-Acting Cabotegravir Plus Rilpivirine Use in People With a History of Adherence Challenges

There are emerging data on the use of LA CAB/RPV in people with a history of adherence challenges. The open-label Long-Acting Therapy to Improve Treatment Success in Daily Life (LATITUDE [ACTG A5359]) Study enrolled people who had HIV viremia, challenges in taking daily oral ART, and no evidence of CAB or RPV resistance.[60] After adherence support and conditional financial incentive, participants who were able to achieve viral suppression were randomized to monthly LA CAB/RPV or to continue on the oral regimen. Study randomization was stopped early by the Data Safety Monitoring Board because of lower rates of virologic failure in individuals randomized to LA CAB/RPV than those staying on oral therapy (see the Virologic Failure section for more discussion).

Optimization Strategies for People With Viral Suppression and a History of NRTI and/or NNRTI Resistance

Some existing data demonstrate the safety and efficacy of select within-class and between-class switches for individuals with underlying drug resistance who are on a stable ARV regimen with suppressed HIV RNA (e.g., for 6 months or longer). These findings are further supported by data extrapolated from those experiencing virologic failure.

Within-Class Switch From Dolutegravir to Bictegravir in the Setting of Limited Resistance

The GS-US-380-4030 study enrolled 565 participants who were stably suppressed on DTG plus two NRTIs. The participants were randomized to either remain on their current regimen or switch to BIC/FTC/TAF. After 48 weeks, the groups had similar rates of sustained suppression. The rates of viral suppression were similar for those with a documented history of NRTI resistance (approximately 25% of participants) and those without a history of NRTI resistance.[61] Results from this trial lend theoretical support to other optimization strategies that include a switch from one high-barrier drug to another in the setting of underlying NRTI genotypic resistance. This study also supports using drugs with a high barrier to resistance when only one, and possibly no NRTIs in the background regimen, need to be fully active. This is further supported by other lines of evidence, some of which are discussed below.

Data of Within and Between Class Switches to Bictegravir in the Setting of Limited Drug Resistance

The BRAAVE study was an open-label, optimization study for Black people with HIV and viral suppression for ≥12 months on a standard regimen of two NRTIs plus a third agent (INSTI, NNRTI, or PI). Individuals were randomized to switch to BIC/FTC/TAF or to remain on current therapy (although individuals on TDF were switched to TAF). Switching to BIC-based therapy was noninferior for maintaining viral suppression compared with continuing current oral therapy. Baseline regimens included 61% INSTI, 31% NNRTI, and 9% PI. Baseline resistance did not affect the outcomes of therapy. In particular, NRTI resistance was present in 14% of participants, with 10% harboring the M184V/I mutation.[62]

Switch From a Boosted Protease Inhibitor to Dolutegravir in Individuals With Viral Suppression and Prior First-Line NNRTI Plus NRTI Failure

The second-line switch to DTG (2SD) study was conducted at four sites in Kenya in a population of people with HIV who had prior first-line NNRTI plus NRTI regimen failure and achieved viral suppression on a current ritonavir-boosted PI-based regimen without undergoing genotypic resistance testing.[63] In this prospective, open-label trial, 795 participants with HIV were randomized 1:1 to switch the boosted PI to DTG or continue the current regimen. NRTIs were not switched, although a switch was allowed if clinically indicated. At Week 48, switching to DTG was noninferior to continuing a boosted PI with about 5% of participants in each arm having viral rebound >50 copies/mL. In the 40 people with virologic rebound, 20 in each arm, no resistance to DTG or PIs was found. Grade 3 or 4 adverse events were similar in the two groups. This study was limited by the absence of genotypic resistance data demonstrating the amount of NRTI resistance present at the time of first-line NNRTI plus NRTI failure. Nevertheless, several related studies in similar settings have demonstrated that extensive NRTI and NNRTI resistance is expected in this situation, often including resistance to tenofovir and 3TC or FTC.[64-66] Accepting that substantial NRTI resistance was likely to be present in this study population, 2SD provided evidence that a person who is suppressed on a boosted PI-based regimen is likely to remain suppressed on a second-generation INSTI-based regimen in the setting of NRTI resistance. This is further supported by data showing that people with virologic failure and NRTI resistance can be successfully treated with second-generation INSTIs plus TAF or TDF and FTC or 3TC.[64]

Data From Virologic Failure Studies Inform Optimization With NRTI Resistance in Clinical Practice

Several studies conducted in resource-limited countries where people with first-line NNRTI-based virologic failure and who have NRTI-resistance support treatment recommendations for optimizing ART in these settings (details in the Virologic Failure section). In the DAWNING study,[67] for individuals who failed first-line NNRTI-based ART, DTG (84%) outperformed LPV/r (70%) for 48-week viral suppression <50 copies/mL. Participants who had one active NRTI in their study regimen had similar virologic responses as those with two active NRTIs. In the NADIA study, participants failing first-line NNRTI-based therapy were randomized to either DTG or DRV/r combined with randomized NRTIs. At enrollment, resistance to NRTIs was common with 86% of participants having an M184V mutation and 50% having a K65R mutation. At 48 weeks, DTG was noninferior to DRV/r, with both groups achieving viral suppression to <400 copies/mL in about 90% of participants. There were no differences in rates of viral suppression between participants with resistance to one or both NRTIs in their regimen compared to those with no NRTI resistance.[64] At Week 96, TDF was superior to zidovudine when combined with 3TC.[68]

Although these were studies of ART use in the setting of initial NNRTI-based virologic failure, we expect that regimens that are effective during viremia would also be effective in the setting of viral suppression in people with similar ARV resistance patterns (NRTI resistance, but no known or suspected PI or INSTI resistance). These studies support that for optimization in the setting of NRTI resistance, two NRTIs (TAF or TDF plus 3TC or FTC) should be included in the regimen with a fully active drug with a high resistance barrier, such as DTG **(AII),** BIC **(BIII),** or boosted DRV (DRV/c or DRV/r) **(BIII).** The use of regimens without any fully active NRTIs **is not routinely recommended** when there are other viable treatment options. However, in some clinical situations—such as when prior resistance testing is not fully available, to avoid major drug–drug interactions, to keep regimens simpler, or for other reasons—a regimen with a fully active drug with a high resistance barrier plus two partially active NRTIs can be considered. Both tenofovir and cytidine analogs may retain partial activity even when resistance is present.

Optimization Strategies for People With Viral Suppression and a History of Complex Underlying Resistance

Before optimizing an ARV regimen of a person with viral suppression who has a history of treatment failure and complex drug resistance, a careful review of the individual's full ARV history and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII).**

As described in the Optimization Strategies for People With Viral Suppression and a History of NRTI and/or NNRTI Resistance section above, any regimen that includes a fully active drug with a high barrier to resistance (e.g., DTG, BIC, or boosted DRV) plus two NRTIs (even if resistance is present), is likely to achieve suppression in those experiencing virologic failure and maintain suppression in the setting of optimization.[63,64] Reliably maintaining suppression when there is not a fully active drug with a high resistance barrier is more complicated and requires careful consideration before any switch is made. In people with prior virologic failure(s) and/or limited prior resistance testing, proviral DNA genotypes can be considered. Clinicians should keep in mind that proviral DNA resistance mutations found will be useful, but some archived resistance mutations may not be found with this testing. Previous studies demonstrated that it is best to include at least 2 (preferably 3) fully active drugs in the setting of virologic failure if a fully active drug with a high resistance

barrier is not included in the regimen due to resistance and/or intolerance.[69] In this setting, it will often require incorporating active drugs in classes other than NRTIs, NNRTIs, PIs, and INSTIs, such as entry inhibitors (i.e., CCR5 antagonists, post-attachment inhibitors, attachment inhibitors, and fusion inhibitors) or capsid inhibitors (e.g., lenacapavir), recognizing that entry and capsid inhibitors have primarily been studied and are indicated for those with virologic failure.

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Discontinuation or Interruption of Antiretroviral Therapy

Updated: January 20, 2022
Reviewed: January 20, 2022

Discontinuation or interruption of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and/or clinical progression.[1-5] Thus, discontinuation or planned interruption of ART is not recommended outside the context of a clinical trial **(AI).** However, unplanned interruption of ART may occur under certain circumstances as discussed below.

Unanticipated Interruptions of Oral Antiretroviral Drugs

Reasons for short-term interruption (days to weeks) of ART vary and may include intercurrent illnesses that preclude oral intake (e.g., gastroenteritis, pancreatitis), surgical procedures, drug toxicity, or interrupted access to antiretroviral (ARV) drugs. Stopping ART for a short time (i.e., less than 1 day to 2 days) usually can be done by holding all drugs in the regimen. Whether unplanned interruptions occur by accident or by necessity (e.g., because of drug toxicities), all efforts should be made to minimize their duration. Recommendations for some specific scenarios are listed below.

When a Patient Experiences Unexpected Inability to Take Solid Oral Medications

For patients who require tube feeding, some ARV drugs are available in liquid formulations, and some pills may be crushed. The Oral Antiretroviral/HCV DAA Administration[6] provides information on crushing pills and formulating liquid ARV drugs. Additional information also may be available in drug product labels. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way for a patient with a feeding tube to continue an effective ARV regimen.

For patients unable to take medications by any enteral route (e.g., in the context of severe gastrointestinal disease), all components of the oral drug regimen should be stopped simultaneously, regardless of half-lives of the drugs. After resolution, all components of the ARV regimen should be restarted simultaneously.

Several ARV drugs are available as parenteral formulations; these include zidovudine, enfuvirtide, ibalizumab (IBA), and the long-acting (LA) injectable formulations of cabotegravir (CAB LA) and rilpivirine (RPV LA). The combination of CAB LA and RPV LA is approved as a complete regimen for the treatment of HIV. However, this regimen has not been studied as an alternative for patients who cannot take oral medications. Clinicians should consult with an HIV specialist before prescribing any of these agents.

When a Patient Experiences a Severe or Life-Threatening Toxicity to an Antiretroviral Agent

All components of the ARV drug regimen should be stopped simultaneously, regardless of drug half-life. After resolution, a different complete regimen that does not include the offending agent should be started.

Interruption of Long-Acting Antiretroviral Drugs

The combination of CAB LA and RPV LA is approved as a complete regimen for the treatment of HIV. CAB LA and RPV LA are given as intramuscular (IM) injections and have extended half-lives. Therefore, patients who miss doses or discontinue therapy without bridging with an oral ARV regimen are at increased risk of virologic failure with development of drug resistance. Clinicians should refer to prescribing information for CAB LA and RPV LA for the management of missed doses or discontinuations.[7] For planned missed injection doses of CAB LA and RPV LA, oral formulations of CAB and RPV should be made available to patients as a bridging therapy for up to 2 months. Oral formulation of RPV is available by prescription in community pharmacies, but oral formulation of CAB is available only through the manufacturer. When stopping long-acting injectable ART, transition to a suppressive oral ARV regimen should occur within 4 weeks of the last planned IM doses. Patients who have missed or delayed clinic visits repeatedly should be reassessed to determine if resumption of injections is appropriate or if they may need to be transitioned back to an oral regimen. Plasma viral load testing should be performed before the transition, and drug-resistance testing should be considered if plasma viremia is present.

Patients with drug-resistant HIV may receive IBA as part of a salvage regimen. IBA is initiated with a 2,000-mg loading dose given as an intravenous (IV) infusion, then followed by 800 mg given as an IV infusion every 14 days as maintenance therapy. If a dose is missed by ≥3 days, a repeat loading dose of 2,000 mg IV infusion is recommended before resumption of maintenance therapy.

Analytical Treatment Interruption

Several research studies are evaluating approaches to achieve sustained ART-free viral remission or a functional cure for HIV.[8] Viral eradication (i.e., elimination of HIV entirely from an individual) remains a more challenging, longer-term goal. Currently, the only way to reliably test the effectiveness of these strategies is to interrupt ART and closely monitor for viral rebound in the setting of a clinical trial, an approach referred to as "analytical treatment interruption" or ATI.[9] The duration of treatment interruption, the dynamics of viral rebound, and the criteria for restarting ART are part of ATI clinical trial designs with the goal to conduct these clinical trials safely.

Before ART is interrupted, participants of ATI trials should be made aware of and understand the risks of viral rebound,[10] acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations (e.g., oral thrush) or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), and the development of drug resistance. Patients should be counseled about the need for close clinical and laboratory monitoring during ART interruptions and provided counseling and linkage to pre-exposure prophylaxis services should they wish to refer sexual partners at risk for acquiring HIV.

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Considerations for Antiretroviral Use in Special Populations

Adolescents and Young Adults With HIV

Updated: June 3, 2021
Reviewed: June 3, 2021

Key Considerations and Recommendations
• Adolescents and young adults (AYA) with HIV largely belong to two distinct groups: those who acquired HIV in the first decade of life and who may be heavily antiretroviral therapy (ART)–experienced (early-acquired HIV); and those who acquired HIV in or after the second decade of life who may be mostly ART-naive. • ART is recommended for **all** AYA with HIV **(AI)** to reduce HIV-related morbidity, mortality, and transmission. • For AYA with HIV who are at risk for poor clinical outcomes, it is critically important to assess the behavioral and psychosocial context, and their ability to adhere to ART. Efforts should be made to provide youth-friendly support and infrastructure to reduce barriers to adherence and maximize success in achieving sustained viral suppression **(AIII).** • Pediatric and adolescent care providers should prepare AYA with HIV for the transition into adult care settings. Adult providers should be knowledgeable about this unique patient population and the challenges that frequently accompany the transition into the adult care setting. Consulting and collaborating with pediatric and adolescent HIV care providers is critical to ensure the successful transition of AYA with HIV to adult providers and continued engagement in care **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Adolescents (13–19 years old) and young adults (20–24 years old) (AYA) with HIV consistently account for about one-fifth of new infections in the United States.[1] AYA with HIV have lower rates of testing, diagnosis, treatment engagement, and viral suppression than adults with HIV. Importantly, unique developmental, psychosocial, behavioral, and infrastructural factors affect this vulnerable population. Without having their specific challenges and needs addressed, AYA with HIV remain at risk for poorer HIV-related outcomes, including persistent viremia, drug resistance, morbidity, mortality, and secondary transmission.

Epidemiology

Globally, approximately 5 million young people aged 15 to 25 years live with HIV.[2] AYA with HIV are mostly individuals who acquired HIV in the first decade of life, mainly perinatally and rarely via blood transfusion or from sexual abuse. During adolescence and young adulthood, most individuals acquire HIV through sexual activity. Among the latter group, the Centers for Disease Control and Prevention (CDC) estimates that consistently one-fifth of the approximately 40,000 individuals newly diagnosed with HIV in the United States annually are adolescents and young adults.[1] The majority of new infections in this age group are among Black/African Americans and Hispanic/Latino males who identify as men who have sex with men (MSM). For example, in 2018, more than 50% of the infections in this age group were among young Blacks and African Americans,

and 27% were among Hispanics and Latinos. Most (87%) were male, with 92% identifying as MSM. Compared to adults with HIV, AYA with HIV are less likely to have acquired HIV from injection drug use, and trends in HIV and AIDS prevalence indicate that the disproportionate burden of HIV among racial and ethnic minorities is even greater among youths 13 to 24 years of age than among those older than 24. Together, AYAWH account for approximately 34,000 of the individuals being followed at pediatric and adult clinics in the United States.[3]

Heterogeneity of Adolescents and Young Adults With HIV

AYA with HIV represent a diverse population in terms of socio-demographics, mode of HIV acquisition, sexual and substance use history, clinical and immunologic status, psychosocial development, and ability to adhere to medications. These distinctions have implications for HIV treatment, including the best ways to support AYA with HIV to optimize outcomes. AYA with HIV largely belong to two distinct groups:

- ***Adolescents and Young Adults With Early-Acquired HIV:*** These individuals, who acquired HIV in the first decade of life, are more likely to be treatment-experienced and have antiretroviral (ARV) drug resistance that may limit their options for ART regimens. This may be even more relevant for AYA with HIV who emigrated from parts of the world where routine viral load and genotypic resistance testing are not as readily available so that recognition of virologic failure and drug resistance may be delayed or missed. Also, individuals in this group generally have undergone a longer duration of disease chronicity and may have greater disease burden and more complications, less functional autonomy, and higher mortality risks.[4]
- ***Adolescents and Young Adults With HIV Acquired Later in Life:*** Individuals in this group are a more heterogeneous group of mostly young men (especially MSM) and young cisgender and transgender women with HIV acquired primarily through sexual activities. A minority in this group have acquired HIV through injecting drugs or were victims of sexual abuse. The intersection of adolescence and young adulthood with other key risk populations (e.g., MSM, people who use drugs, transgender individuals) magnifies the risk of poor clinical outcomes in this younger population. A statistically higher percentage of individuals in this group reported experiencing an even more extensive number of negative life experiences compared to those who acquired HIV early in life (38.8% versus 16.3%, $P<.012$).[5]

Unique Characteristics and Considerations for Adolescents and Young Adults With HIV

Although a diverse group, many AYA with HIV share unique characteristics that distinguish them from adults with HIV. Furthermore, AYA with HIV have certain commonalities that, while not necessarily unique to youth, disproportionately affect their chances of successful HIV treatment. Compared to adults 25 years old and older, AYA with HIV have poorer outcomes on each step of the HIV care continuum[6] (i.e., HIV diagnosis, linkage to HIV care, receipt of care, retention in care, achievement of viral suppression, maintenance of viral suppression). Most notably, only 40% of AYA with HIV are aware of their diagnosis and only 6% to 30% are virally suppressed.[7] These numbers are significantly worse than documented in older adults with HIV.[8] In one study of MSM of all ages, the percentage of those linked to HIV care within one month of diagnosis was lowest among AYA with HIV aged 13 to 19 (69%) and 20 to 24 (70%) years.[9] This group also had the lowest rates of retention in care and viral suppression. Older young adults (through age 29), who currently have

the highest incidence of HIV infection among all age groups, have similar challenges, with 30% unaware of their infection status. They, too, require focused attention.

There are myriad reasons AYA with HIV do not perform as well on the HIV care continuum and are at greater risk of poorer clinical outcomes than adults with HIV. Perhaps most important, AYA with HIV often do not have the same developmental capacity or ability to secure resources as their adult counterparts. These key features, discussed below, should be considered carefully because they can negatively affect HIV treatment and may alter clinical decision-making.

Adolescents and Young Adults With HIV as a Developmentally Distinct Patient Population

Developmental maturity in AYA with HIV generally can be grouped into several, often overlapping, areas, including physical, cognitive, communication and language, and social and emotional, combined with an emerging recognition of sexual identity. Several overarching factors—especially HIV-related stigma, discrimination, and a fear of familial and/or social rejection—can contribute to impaired development in all areas and adversely affect HIV treatment and clinical outcomes for many AYA with HIV. Additional important psychosocial factors discussed below commonly are seen in this population and also can affect development and successful HIV treatment.

Key developmental factors that may impact HIV treatment are highlighted below:

- ***Cognitive development:*** Evolving cognitive processes, which normally continue well into the third decade of life, are particularly relevant to HIV treatment in AYA with HIV. Their developing decision-making capacity often is driven by concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to fit in with their peers, all of which can affect HIV treatment negatively, including medication adherence and long-term clinical outcomes.[4,10,11] Likewise, AYA with HIV are at risk for neurocognitive impairment and mental health comorbidities,[12-15] including psychiatric, behavioral, and substance use disorders, which can further affect cognitive development and compromise effective HIV treatment.
- ***Physical development:*** The rapid physiologic changes (e.g., puberty, rapid growth) that occur in adolescence may result in altered ARV pharmacokinetics, underscoring the importance of adolescent-specific studies.[4] AYA with HIV, particularly those with infection acquired early in life and/or while sexually immature, also are at risk for impaired physical development, especially delayed sexual maturation and impaired normal bone development, which may have long-term consequences like reduced final height and peak bone mass, the latter being a key risk factor for developing osteoporosis.[16] Both delayed maturation and short stature may increase anxiety, depression, and stigma, which may, in turn, affect treatment adherence.[17] AYA with HIV who acquire HIV later in life still may be affected because peak bone mass is not achieved until around age 30. A small study showed lower bone mass in Tanner Stage 5 young men aged 20 to 25 years who acquired HIV during adolescence than in HIV-uninfected age-matched controls.[18]

Thus, developmental maturity should be considered in AYA with HIV, because associated clinical implications may alter HIV treatment decisions, including ARV selection and dosing.

Psychosocial and Related Risk Factors Affecting Adolescents and Young Adults With HIV

Several psychosocial, behavioral, and environmental risk factors affect many AYA with HIV and can undermine successful HIV treatment disproportionately in this population. Common key risk factors are summarized here:

- ***Mental and behavioral health:*** The percentage of AYA with HIV with behavioral and mental health conditions is very high and can undermine engagement in care and medication adherence. The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention deficit hyperactivity disorder. Among adolescents with early-acquired HIV, nearly 70% meet criteria for a psychiatric disorder at some point in their lives.[13,19-21] Similarly, depression and anxiety were identified by symptom inventory 43% and 31% of the time, respectively, among AYA with HIV presenting for care at treatment sites in the Adolescent Trials Network.[22]
- ***Substance use:*** Substance use is prevalent among AYA with HIV. Among more than 2,000 AYA with HIV (72% acquiring HIV later in life) surveyed by the Adolescent Trials Network, weekly or more frequent use of tobacco (33%), marijuana (28%), alcohol (21%), and other illicit drugs (23%) was reported.[23,24] Young MSM had higher odds of each substance use behavior, whereas transgender women had increased odds of marijuana and other illicit drugs. Suboptimal ART was associated with increased risk of substance use behaviors,[24] underscoring the need to screen for and address substance use to improve treatment outcomes.
- ***Transgender AYA with HIV:*** About 1 in 3 new HIV diagnoses among transgender individuals are among those aged 13 to 24 years.[25,26] Transgender AYA with HIV report high rates of stigma and other structural and logistical barriers that affect their access to gender-affirming care, as well as HIV prevention and treatment services, which are known to be associated with retention in care and adherence to treatment (see Transgender People with HIV).
- ***Homelessness and unstable housing:*** Among the 4.2 million homeless adolescents and young adults in the United States (of whom 700,000 are unaccompanied minors)[27] , the estimated HIV prevalence ranges from 3% to 16%. Youth who identify as lesbian, gay, bisexual, transgender, or queer (LGBTQ); those with mental health concerns; and those who engage in substance use are disproportionately represented among homeless youth.[28] Homeless and unstably housed AYA with HIV have greater difficulties securing and sustaining resources and engaging in and being retained in care and treatment.[29]
- ***Additional social and environmental factors:*** A number of social and environmental factors commonly found among AYA with HIV negatively affect their HIV treatment, including limited familial and/or social support, lack of health insurance and/or experience with health care systems, unstructured and chaotic lifestyles, transportation barriers, food insecurity, limited educational opportunities, limited employment opportunities and/or unstable employment, and a history of trauma and/or sexual abuse.[30]

Optimizing Treatment Effectiveness and Supporting Adherence in Adolescents and Young Adults With HIV

Given the unique physiologic, developmental, and psychosocial characteristics discussed above, AYA with HIV require comprehensive systems of care with culturally competent providers and tailored treatment to serve all their specific medical and psychosocial needs. To maximize their chances of success, it is also imperative to routinely assess each AYA with HIV for individual factors that may need to be addressed or considered in treatment decisions or that may affect adherence.

Table 13 summarizes common adherence barriers among AYA with HIV, along with recommended support strategies. Refer to the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection and the Adherence to Antiretroviral Therapy in Children and Adolescents with HIV

additional approaches. Targeted interventions to improve treatment effectiveness and adherence related to a few key psychosocial factors among AYA with HIV also are highlighted here:

- ***Mental health care:*** Strategies to improve the provision of mental health care for AYA with HIV are critically important for optimizing treatment for co-occurring HIV and mental health problems.[31] These strategies include improving provider education, integrating trauma-informed care practices, increasing access to mental health professionals through colocated services for HIV care, expanding care delivery paradigms like telemedicine, and optimizing treatment approaches. An example of the latter is a combination of tailored psychotherapy and pharmacotherapy.[26,32] Further guidance for providing appropriate mental health care for AYA with HIV can be found in the Pediatric Guidelines.
- ***Substance use disorders:*** Providers should assess and recommend treatment for substance use disorders, with consideration of emerging substance use trends, such as the use of electronic vapor products. Further guidance for providing appropriate substance use screening and treatment for AYA with HIV can be found in the Pediatric Guidelines and in the Substance Use Disorders and HIV section.
- ***Transgender AYA with HIV:*** Providers must increase their understanding of this population to minimize barriers and optimize testing, engagement, and outcomes for transgender AYA with HIV. Drug-drug interactions between hormonal therapy and ART can occur but are less common with newer ART regimens. Further information can be found in the Transgender People with HIV section and Adolescent Trials Network Transgender Youth Resources.[33]
- ***Psychosocial and environmental stressors:*** Multimodal interventions that enhance social support and teach adaptive coping skills may help AYA with HIV manage environmental stressors and improve clinical outcomes.

Specific Antiretroviral Therapy Considerations in Adolescents and Young Adults With HIV

All AYA with HIV should initiate ART as soon as possible and stay on ART indefinitely to maximize viral suppression, reduce morbidity and mortality, and prevent secondary HIV transmission **(AI)**. As described below, clinicians should consider simplifying ART regimens and using antiretrovirals with high barriers to resistance whenever possible to support adherence.

Strategies to Improve Medication Adherence

Clinicians selecting ART for AYA with HIV must balance the goal of prescribing a maximally potent regimen with a patient-by-patient assessment of existing and potential adherence barriers and available youth-friendly support strategies to facilitate adherence.[34] Additional considerations and strategies that may affect adherence among AYA with HIV are highlighted below in **Table 11.**

Table 11. Antiretroviral Therapy–Specific Strategies to Improve Medication Adherence

Antiretroviral Therapy-Specific Strategies to Improve Medication Adherence	
Regimen selection	• Simple ART regimens (e.g., fixed-dose, once daily combinations) with high barriers to resistance are preferable, if possible.[35] • Minimal side effects (e.g., gastrointestinal)
Treatment plan	• Develop the plan in partnership with AYA with HIV, considering daily schedule; tolerance of pill number, size, and frequency; issues affecting absorption; and potential adverse effects and interactions with other medications.[34,36] • Design adolescent-friendly reminder systems[37] (e.g., apps, cell phone reminders, pill boxes) for adherence support.[38]
Motivators	• Emphasize personal benefits (e.g., viral suppression, improved health). • Undetectable equals untransmittable (U=U) status disclosure to sexual partners without HIV may act as a particularly strong motivator for reducing stigma and improving adherence among AYA with HIV.

Antiretroviral Therapy Regimens for Adolescents and Young Adults With HIV Without Drug Resistance

The boosted protease inhibitor (PI) darunavir (DRV) and the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) and bictegravir (BIC) offer once-daily dosing. When coformulated with a dual nucleoside backbone, they also provide single-tablet regimens with high genetic barriers to resistance.

Clinical trials have demonstrated the superiority of DTG over boosted PI-based regimens. BIC coformulated with tenofovir (TAF) and emtricitabine (FTC) also appears to have a low risk of treatment-emergent resistance and is available as a single-tablet regimen with a small pill size and no food requirements. BIC is currently licensed for use in children or adolescents ≥25kg. Adolescent studies are ongoing with an adult fixed-dose combination of BIC/FTC/TAF from 12 years of age and 35 kg with a favorable interim analysis in a stable adolescent switch study.[39]

A two-drug once-daily single-tablet regimen of DTG/lamivudine is recommended as an initial ART regimen except for individuals with HIV RNA >500,000 copies/mL, hepatitis B virus (HBV) coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Long-acting formulation regimens, the first of which (cabotegravir/rilpivirine) was recently FDA-approved in the United States, are considered a viable option for patients who are engaged in care, virologically suppressed on oral therapy, and agreeable to the administration schedule. These agents are being studied for AYA with HIV[40] ages 12 to 17 without relevant antiretroviral drug resistance. Case reports of viral suppression with the use of long-acting rilpivirine (RPV) and cabotegravir (CAB)[41] in AYA with HIV with a history of poor adherence are encouraging (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression). Studies to evaluate these modalities among nonadherent AYA with HIV are under development.[42]

Antiretroviral Therapy–Experienced Adolescents and Young Adults With HIV with Drug Resistance

AYA with HIV who acquired HIV early in life often have treatment challenges associated with the long-term use of ART that mirrors those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects. In ART-experienced adolescents, DTG was safe and well tolerated, and it achieved viral suppression rates of 44% to 66% when combined with an optimized background regimen. Acquired treatment-emergent INSTI resistance may occur.[43] For adolescents with dual-class resistance, the introduction of DRV/cobicistat/FTC/TAF in combination with DTG offers the potential of a potent triple-class regimen with a high genetic barrier to resistance with only two pills once daily[44] (see Virologic Failure and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression).

Antiretroviral Therapy Considerations in Sexually Immature Adolescents and Young Adults With HIV

The physiologic changes (e.g., puberty, rapid growth) that occur in adolescence may result in altered pharmacokinetics. Therefore, although generally it is appropriate for postpubertal adolescents to be dosed with ARV drugs according to adult guidelines, adolescents in early puberty should be dosed according to the Pediatric Guidelines, which factor in dosages by weight and sexual maturity ratings.

Additional Antiretroviral Therapy Considerations in Adolescents and Young Adults With HIV

Additional considerations include an increased risk of side effects, such as bone and renal toxicity with tenofovir-based drugs in the rapidly growing adolescent. These concerns are magnified in low-weight adolescents for whom appropriate lower-dose formulations are not available. Because AYA with HIV have not yet reached peak bone mass, TAF generally should be used instead of TDF, because of a greater bone loss with the latter ARV.

For a more detailed discussion on ART therapy in AYA with HIV, please see the What to Start section and the Pediatric Guidelines. For additional information on treatment adherence in AYA with HIV, please see Table 18, Adherence to the Continuum of Care, and the Pediatric Guidelines.

Preventive Measures and Supporting Long-Term Health in Adolescents and Young Adults With HIV

People with HIV are at an increased risk of HIV- and ART-related comorbidities, including cardiovascular disease, diabetes, metabolic syndrome, osteoporosis, and neurocognitive impairment. When HIV is acquired at birth or early in life, an individual can live for many decades with the condition. However, engagement in health-risk behaviors (e.g., tobacco smoking, alcohol and drug use, unhealthy diet, physical inactivity) may have greater long-term implications for clinical outcomes in this population.

Preventive health care and promotion of positive health behavior during the critical time of adolescence and young adulthood can shape future habits and clinical outcomes over a lifetime. Incorporating regular screening, preventive health care, and health education is critical for optimizing short- and long-term physical and mental well-being and should be considered part of routine HIV treatment. Careful attention should be paid to modifiable risk factors in these early decades, such as weight gain and obesity, dyslipidemia, vitamin D deficiency, and tobacco use. Aggressive screening

and risk factor mitigation early in the life of AYA with HIV not only improves current health but also can decrease their risk of developing comorbidities later in life. See HIV Medicine Association of the Infectious Diseases Society of America HIV primary care guidance for more details.

Transitioning to Adult HIV Care

Given lifelong infection with HIV and the need for treatment throughout the life course, HIV care programs and providers need flexibility to transition care appropriately for AYA with HIV. A successful transition requires an awareness of fundamental differences between many adolescent and adult HIV care models.

In most adolescent HIV clinics, care is more teen-centered and multidisciplinary, with primary care highly integrated into HIV care.[45] Often there is anonymity, with clinics not being devoted specifically to HIV or infectious diseases. Moreover, such services as sexual and reproductive health and mental health care are often found in one clinic setting (i.e., the medical home). Additionally, these clinics are more likely to be "youth-friendly" by including such aspects as waiting areas where AYA with HIV can access computers and other items that may facilitate engagement; flexible schedules that include evening hours or walk-ins; technology like social media and texting to engage patients; staff who are trained specifically in the unique cognitive, developmental, and other psychosocial aspects of AYA with HIV; and lower patient-to-provider ratios. In contrast, some adult HIV clinics may be more HIV-specific and rely more on referral of the patient to separate subspecialty care settings, such as gynecology.[46] Furthermore, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients.

Transitioning the care of an AYA with HIV must consider such factors as medical insurance; degree of independence, autonomy, and decision-making capacity; patient confidentiality; and informed consent. Nonetheless, given the structural limitations (adolescent clinics not being able to see patients over a certain age), care transitions must occur, usually between the ages of 21 and 25. The period of transition is a highly vulnerable time for attrition from HIV care. Data on transition outcomes are emerging, showing variable rates of successful transition to adult care ranging between 50% and 85%.[47-50]

It is important to recognize that the transition for AYA with HIV with early-acquired HIV versus those who acquired HIV later in life may pose distinct challenges. AYA with HIV who acquired HIV early in life—who often have experienced significant instability and prior loss—may experience the transition to adult HIV care as yet another traumatizing event. Alternatively, those who acquired HIV later in life, given their more recent engagement in the medical system, may be less likely to be effectively engaged in pediatric and adolescent care, which may affect their ability to transition successfully. Factors to date that have been associated with successful transition for those with early-acquired HIV include high self-management and perceived emotional and social support.[51]

To maximize the likelihood of a successful transition, interventions to facilitate transition are best implemented early on.[49,52-54] Strategies and approaches for both the adult and pediatric and adolescent programs are discussed below:

Table 12: Approaches to Optimize Care Transition for AYA With HIV

Pediatric/Adolescent	Adult
Personnel	
• Engage a multidisciplinary team knowledgeable about medical and psychosocial issues of AYA with HIV, including the challenges of transitioning youth to adult care settings. • Utilize combined internal medicine and pediatrics-trained providers if available. • Assign a transition point person and have their contact information readily available. • Educate HIV care teams and staff about transitioning AYA with HIV and their needs.	• Engage a multidisciplinary adult care team knowledgeable about medical and psychosocial issues of AYA with HIV, including the challenges of transitioning youth to adult care settings. • Utilize combined internal medicine and pediatrics providers if available. • Assign a transition point person and have their contact information readily available. • Identify outreach specialists, navigators, social workers, case managers, and providers with a youth-friendly approach. • Educate clinic personnel about AYA with HIV and their challenges to enhance sensitivity and understanding and minimize stigma.
Education and Preparation of AYA with HIV	
• Enhance AYA with HIV health literacy, including understanding of HIV and their medical history. • Address patient and family resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles. • Help youth develop life skills, including, but not limited to, counseling on appropriate use of a primary care provider and how to manage appointments; the importance of prompt symptom recognition and reporting; and self-efficacy in managing medications, insurance, and assistance benefits.	• Meet AYA with HIV before transition, if possible. • Clearly outline policies and expectations before and during the first visit. • Have an orientation plan to acquaint newly transitioned AYA with HIV to the clinic environment and adult clinical care program. • Implement interventions that may improve outcomes, such as patient navigators, peer support groups, mental health assessment, and inclusion of parents and guardians where available. • Address health literacy and ensure AYA with HIV understand HIV, goals of care, etc. • Continue to work with AYA with HIV toward developing life skills, etc.

Table 12: Approaches to Optimize Care Transition for AYA With HIV

Pediatric/Adolescent	Adult
Strategies and Approaches	
• Identify adult care providers able to provide youth-friendly care for adolescents and young adults. • Develop a formal, purposeful individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning to adult HIV care. • Optimize provider communication between adolescent and adult clinics, including a warm multidisciplinary, comprehensive medical history hand-off that includes prior regimens and outcomes (e.g., adherence, virologic failure and resistance).	• Develop a realistic clinic model based on specific needs (e.g., simultaneous transition of mental health and/or case management versus a gradual phase-in) and staffing. • Engage in a warm handoff from the pediatric team, which allows the accepting adult team to learn about and understand the multidisciplinary challenges and goals for the patient. Devise a plan for how to continue building the skills on the adult side. • Build in flexibility (e.g., permissive grace period for appointments, leniency for missed appointments, particularly when first transitioning). • Incorporate other aspects of care beyond HIV management, if possible (e.g., family planning, sexually transmitted infection testing and treatment, mental health, substance use).
Communication	
• Foster regular dialogue between pediatric and adolescent and adult teams before and after transition through regular meetings, case conferences, etc. • Solicit feedback from the AYA with HIV • Use technology (e.g., texting, HIPAA-compliant messaging apps, telemedicine).	
Evaluation	
• Implement ongoing evaluation to measure the success of the selected model (retention in adult care).	

Discussions regarding transition should begin early and before the actual transition process.[55] Attention to the key interventions noted above will be likely to improve adherence to appointments and avoid the potential for youth to fall through the cracks, as this concept is referred to commonly in adolescent medicine. For a more detailed discussion on specific topics related to transitioning care for adolescents and young adults, see Transitioning into Adult HIV Care. Please also refer to the Pediatric Guidelines.

Table 13: AYA With HIV ARV Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
Prioritization of short-term goals and socialization with peers over daily HIV treatment adherence	Youth-friendly reminder systems (e.g., text, phone, apps)	• Daily adherence to ARV regimens may not take priority in the lives of AYA with HIV. • AYA with HIV benefit from reminder systems to facilitate adherence.
	Novel ART delivery strategies (e.g., long-acting oral or injectable ARVs)	• AYA with HIV show interest in long-acting alternatives for ART delivery. • Long-acting ARVs are a promising tool to facilitate adherence, once approved for AYA with HIV.
Social concerns related to loss of confidentiality	Simple ARV regimens	• Adolescents do not want to be different from peers; adherence to complex regimens is particularly challenging. • Simple ARV regimens are preferable for AYA with HIV.
	User-friendly and discreet regimens	• Avoidance of HIV-related stigma and of unintentional disclosure of HIV status is a priority for AYA with HIV. • Protect confidentiality with user-friendly and discreet adherence supports (e.g., discreet pill bottles, reminder systems, etc.).
Side effects/fear of side effects	ARV regimens that minimize side effects	• Side effects are associated with nonadherence to ARVs. • Regimens with minimal side effects and medications that manage side effects have utility for AYA with HIV.
Denial or dismissal of HIV diagnosis	Motivational interviewing (MI) and motivational enhancement therapy (MET)	• MI and MET acknowledge AYA with HIV's autonomy and potential ambivalence about treatment adherence. • MI and MET have shown promise for improving adherence to chronic disease treatment, including HIV.
	Positive affirmation messages (e.g., text, app)	• Electronically delivered positive affirmation messages can improve self-esteem and ARV adherence among AYA with HIV.
Lack of health literacy regarding the benefits of ART	Health literacy support and U=U education	• AYA with HIV may not fully understand the importance of taking ARVs daily, particularly when they are asymptomatic. • Increased health literacy is associated with better adherence to ARV regimens. • U=U education holds promise for AYA with HIV.

Table 13: AYA With HIV ARV Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
Mistrust of providers and the medical establishment	Empathetic and patient-centered communication	• Communication exploring the needs of AYA with HIV patients can build trust, including exploring needs not directly related to HIV treatment (e.g., school, employment, relationships, etc.).
Mental health and/or substance use	Individualized mental health and substance use services	• Comprehensive mental health and substance use services have shown promise for improving viral suppression among AYA with HIV. • Service should be delivered based on individualized needs assessments.
	Directly observed therapy may be considered	• For some AYA with HIV with difficult adherence problems, directly observed therapy may be considered.
Lack of familial and social support	Family and peer support groups	• Family members and peers are a defense against stigma and social isolation, source of emotional support, and partners in medication management. • Family and peer support groups have utility for AYA with HIV living with HIV.
Provider views of AYA with HIV as "risky" and/or not ready for ART	Promote development of a positive rather than risk-centered identity among AYA with HIV	• Adolescence and young adulthood are periods of identity development where HIV stigma is particularly problematic. • Providers should not conceptualize AYA with HIV as "high risk" to reduce stigma and improve ARV adherence.
Provider implicit biases of AYA with HIV	Implicit bias training	• Consciously changing biased associations and repeated bias self-regulation training can reduce providers' implicit biases.
	Gender-affirming care	• Transgender individuals are more likely to achieve viral suppression when HIV care providers affirm their gender (e.g., use chosen name and pronoun). • For a more detailed discussion, see guidelines for Transgender People with HIV.

Table 13: AYA With HIV ARV Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
Lack of youth-friendly services	Dedicated youth HIV clinic	• Clinic days or hours dedicated to AYA with HIV patients better address unique adherence needs; youth-friendly services include the following: ○ flexible hours, easy scheduling, telephone/telehealth appointments; ○ providers trained in working with AYA with HIV; ○ youth-friendly waiting rooms and physical spaces; ○ supplemental services that comprehensively address psychosocial and health needs of AYA with HIV; and ○ incentives for AYA with HIV care engagement.
	Youth-friendly hours, staff, and physical space	• Where dedicated hours and services are not possible, youth-friendly service elements can be integrated into existing clinic structures, e.g.: ○ offering evening hours; ○ staff training on service delivery to AYA with HIV; and ○ youth-friendly waiting rooms and physical spaces.
	Referrals to more youth-friendly HIV providers	• Where youth-friendly services are not possible, referrals to more youth-friendly HIV care providers should be considered. • Referral decisions should be made collaboratively with the patient.
Lack of comprehensive services that address common psychosocial stressors	Supplemental health, behavioral health, and psychosocial support services	• Individualized delivery of comprehensive supplemental services helps address unique needs of AYA with HIV, including the following: ○ primary care and sexual and reproductive health services; ○ behavioral health services; and ○ psychosocial support services (e.g., school support, transportation, support groups, housing and food assistance).
	Collaboration with and referrals to outside support services	• Where delivery of comprehensive supplemental services is not possible, collaborations with and referrals to outside support services should be considered.

Key: ART = antiretroviral treatment; ARV = antiretroviral; AYA = adolescent and young adult; U=U = undetectable equals untransmittable

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Early (Acute and Recent) HIV Infection

Updated: September 12, 2024
Reviewed: September 12, 2024

Panel's Recommendations

• Antiretroviral therapy (ART) is recommended for all people with HIV, including those with early[a] HIV infection **(AI).** ART should be initiated as soon as possible after HIV diagnosis **(AII).**
• The goals of ART are to suppress plasma HIV RNA to undetectable levels **(AI),** prevent transmission of HIV **(AI),** and preserve immune function **(AIII).** Monitoring of plasma HIV RNA levels, CD4 T lymphocyte cell counts, and antiretroviral (ARV) drug-related adverse effects should be done as recommended for people with chronic HIV infection **(AII).**
• A blood sample for genotypic resistance testing should be sent to the laboratory before initiating ART **(AIII).**
  ○ Standard genotypic drug-resistance testing should be performed for mutations in the reverse transcriptase and protease genes **(AIII)** for all people with early HIV**.**
  ○ Genotype testing for integrase strand transfer inhibitor (INSTI) resistance should be performed for those who acquire HIV during or after the use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), if transmitted integrase stand transfer inhibitor (INSTI) resistance is suspected, or if HIV diagnosis occurs after receiving an INSTI-based regimen for post-exposure prophylaxis (PEP) **(AIII).**
• ART can be initiated before drug-resistance test results are available.
  ○ For those without a history of using CAB-LA as PrEP, one of the following ARV regimens is recommended[b] **(AIII):**
  ▪ Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  ▪ Dolutegravir (DTG) with (TAF or tenofovir disoproxil fumarate [TDF])[c] plus (FTC or lamivudine [3TC])
  ○ For those with a history of CAB-LA use as PrEP, genotype testing before starting ART should include screening for INSTI-resistance mutations **(AIII).**
  ▪ A regimen of cobicistat- (COBI)[d] or ritonavir-boosted darunavir (DRV) with (TAF or TDF)[b] plus (FTC or 3TC) is recommended while awaiting the results of the genotype testing **(AIII).**
  ▪ Use of an empiric INSTI-containing regimen **is not recommended** unless genotype testing shows no evidence of INSTI resistance **(AIII).** This is because INSTI resistance may be present in those who acquire HIV during and possibly after the use of CAB-LA as PrEP.
• In people with HIV RNA levels ≥200 copies/mL and who are taking PrEP, immediate initiation of an effective HIV treatment regimen is recommended while awaiting confirmation of HIV diagnosis **(AIII).**
• Pregnancy testing should be performed in people of childbearing potential before initiating ART **(AIII).**
• When the results of drug-resistance tests are available, the treatment regimen can be modified if needed **(AII).**
• Providers should inform individuals starting ART of the importance of adherence in achieving and maintaining viral suppression **(AIII).**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

[a] Early infection represents either acute or recent (≤6 months) infection.

[b] Because of the low rates of transmitted INSTI resistance in the United States at present, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started while awaiting the results of the INSTI genotype.

[c] TAF and TDF are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

[d] COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been reported during the second and third trimesters.

Introduction

Acute HIV infection occurs soon after transmission and is typically characterized by the lack of anti-HIV antibodies and the presence of viremia, which can be detected by an HIV RNA test or p24 antigen test. Recent HIV infection is considered the period of ≤6 months after infection during which anti-HIV antibodies become detectable. Throughout this section, the term "early HIV infection" is used to refer to either acute or recent HIV infection. People with acute HIV infection may experience fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms; however, illness is generally nonspecific, and people can be asymptomatic or experience relatively mild symptoms.[1-6] Clinicians may fail to recognize acute HIV infection because its manifestations are similar to those of many other viral infections, such as COVID-19, influenza, and infectious mononucleosis. Table 14 below provides clinicians with guidance to recognize, diagnose, and manage acute HIV infection.

Diagnosing Acute HIV Infection

Health care providers should consider a diagnosis of acute HIV infection in a person who has a suggestive clinical syndrome or in asymptomatic individuals who report recent engagement in activities that may put them at high risk of HIV acquisition (see Table 14 below).[7] Individuals may not always disclose high-risk activities or perceive that such activities put them at risk for HIV acquisition. Thus, even in the absence of reported high-risk activities, health care providers should have a low threshold for considering a diagnosis of acute HIV infection. Health care visits to emergency departments provide an opportunity for health care providers to screen for acute or established HIV infection, as well as other sexually transmitted infections. Since 2019, the United States Preventive Services Task Force has recommended routine screening for HIV in adolescents and adults aged 15 to 65 years (Grade A recommendation). Testing of remnant blood specimens from an emergency department identified acute HIV infection in approximately 5 of 499 (1%) people presenting with flu-like symptoms.[8] Acute HIV infection was also diagnosed in 7 of 563 (1.2%) people presenting for evaluation of possible mononucleosis with negative heterophile antibody tests.[9] A study of HIV screening in nine emergency departments in six U.S. cities found that a new HIV diagnosis was made in 0.4% of 214,524 adolescents and adults, of whom 14.5% had acute HIV infection.[10] Current statistics on the prevalence of HIV in geographical areas in the United States can be found on the AIDSVu and Centers for Disease Control and Prevention (CDC) AtlasPlus websites.

The recommended initial laboratory HIV testing algorithm includes combination immunoassays that detect HIV-1 and HIV-2 antibodies, as well as HIV p24 antigen (Ag/Ab assays),[11] primarily due to their enhanced ability to detect acute HIV infection. Specimens that are reactive on an initial Ag/Ab assay should be tested with an immunoassay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are reactive on the initial assay and have either a negative or indeterminate antibody differentiation test result should be tested for quantitative or qualitative HIV RNA; an undetectable HIV RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV RNA in this setting indicates that acute HIV infection is highly likely.[11] People presenting to care during the earliest days following HIV infection may have yet to develop a positive p24 Ag

response, which typically occurs with viral load levels of >20,000 to 30,000 copies/mL. In clinical settings with a high probability of infection, quantitative or qualitative HIV RNA testing should be considered even if the HIV Ag/Ab test result is negative. HIV infection should be confirmed by repeat quantitative HIV RNA testing or subsequent testing to document HIV antibody seroconversion. People who receive antiretroviral therapy (ART) during acute or very early HIV infection may demonstrate weaker reactivity to screening antibody assays or incomplete HIV antibody evolution; may remain non-reactive to confirmatory antibody assays; and in the setting of sustained virologic suppression, may have complete or partial seroreversion.[12-16]

Providers should be aware that even a low-positive quantitative HIV RNA level (e.g., <200 copies/mL but detectable) in the setting of a negative or indeterminate antibody test result is consistent with acute HIV infection. When a low-positive quantitative HIV RNA test result is present at this level, the HIV RNA test should be repeated on a new blood specimen to confirm the diagnosis. Repeated false-positive HIV RNA test results are unlikely.[2] HIV RNA levels in acute infection are generally very high (e.g., >100,000 copies/mL)[1,2,4]; however, levels may be <200 copies/mL in the earliest weeks following infection as viral load continues to rise. In rare cases, however, such low HIV RNA levels also may represent a false-positive result. The previously proposed threshold of <3,000 copies/mL is based on historical data, which used laboratory methods that are now considered obsolete.[17] Improvements in plasma viral load methodology suggest that any positive result on a quantitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result may be consistent with acute HIV infection. Some health care facilities may still be using HIV testing algorithms that test only for anti-HIV antibodies. In such settings, when acute HIV infection is suspected in a person with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV RNA test result (<200 copies/mL)[18] indicate that acute HIV infection is highly likely.

Diagnosing Acute HIV Infection in People Taking Pre-Exposure Prophylaxis

Three antiretroviral (ARV) options—oral emtricitabine (FTC) with either tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) and intramuscular long-acting cabotegravir (CAB-LA)—are now available for HIV pre-exposure prophylaxis (PrEP). People who acquire HIV while taking PrEP may sometimes have ambiguous HIV test results. A positive HIV Ag/Ab test result or a positive HIV RNA test result in the setting of a negative HIV antibody test result should prompt immediate confirmation of HIV diagnosis. It is important to collect a new blood specimen to verify the HIV diagnosis before initiating ART. Important considerations include the following:

- In people with HIV RNA level ≥200 copies/mL who are taking PrEP, immediate initiation of an effective HIV treatment regimen[18] is recommended while awaiting confirmation of HIV diagnosis **(AIII).**

- In people taking PrEP who have a negative HIV antibody test result and a low-positive quantitative HIV RNA test result (<200 copies/mL), a confirmatory HIV antibody test and repeat quantitative plasma HIV RNA test should be performed, and results should be available before initiating ART.

- In rare cases, particularly when PrEP is transitioned to an ARV regimen and HIV RNA and antibody diagnostic testing are inconclusive, HIV DNA testing may be of value.[19] Options for

confirming HIV infection and managing such cases are areas of evolving science summarized by the CDC.[19] Clinicians seeking urgent advice can contact the Clinical Consultation Center's PrEP Service at 1-855-HIV-PREP (or 1-855-448-7737).

Acute HIV Infection in People Taking Long-Acting Cabotegravir for Pre-Exposure Prophylaxis

In the HPTN 083 trial, a pivotal trial of CAB-LA versus TDF/FTC for HIV PrEP with more than 2,000 participants enrolled in each arm, 25 incident cases of HIV were identified in the CAB-LA arm compared to 72 cases in the TDF/FTC arm.[20,21] Selection of a potent ARV regimen in people who develop acute HIV infection while taking CAB-LA for PrEP should consider that injectable cabotegravir (CAB) may remain detectable after treatment discontinuation, for up to 3 years in men and 4 years in women.[22] This long pharmacokinetic tail may contribute to the selection of drug-resistant variants in the setting of incident infection. In an extended analysis of HPTN 083, 34 cases of HIV infection were reported in the CAB-LA arm, with 6 of these cases occurring despite on-time CAB-LA injections.[23,24] Detection of HIV infection was delayed in 15 of 32 cases and was associated with waxing and waning HIV Ag/Ab, HIV antibody, and qualitative and quantitative HIV RNA test results (i.e., fluctuating between reactive/non-reactive, detectable/non-detectable).[23] Major resistance to an integrase strand transfer inhibitor (INSTI) occurred in 10 of the 32 cases evaluated. All 10 participants with INSTI resistance in the CAB-LA arm received their last CAB dose within 6 months of their initial HIV-positive site visit. While the risk of acquired INSTI resistance appears to wane after 6 months, this trend is based on few observations. These data reinforce the importance of screening for INSTI-resistance mutations when acute HIV infection is diagnosed in people taking CAB-LA or with a history of prior CAB-LA PrEP use **(AIII).**

Treating Early HIV Infection

The goals of ART during early HIV infection are to suppress plasma HIV RNA to undetectable levels **(AI),** prevent the transmission of HIV **(AI),** and preserve immune function **(AIII).**[25-27] Importantly, as with chronic HIV infection, an individual's barriers to ART adherence and appointments should be assessed at the time of ART initiation (see Adherence to the Continuum of Care). ART should be initiated as soon as possible after a positive qualitative or quantitative HIV RNA test result **(AII).** Same-day or rapid ART initiation in people with acute HIV has been shown to be safe, acceptable, and effective.[28] It is important to collect a new blood specimen for a confirmatory HIV antibody test and quantitative plasma HIV RNA test to verify the HIV diagnosis. Given the sensitivity of current HIV RNA assays,[29] a positive result by quantitative or qualitative plasma HIV RNA testing in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. HIV treatment does not need to be delayed while awaiting confirmation of HIV diagnosis. Some individuals may not accept their diagnosis or may decline ART initially for other reasons. Individuals who do not begin ART immediately should be maintained in care, and every effort should be made to initiate therapy as soon as they are ready.

Clinical trial data indicate that individuals who are treated during early HIV infection may experience immunologic and virologic benefits.[26,30-41] In addition, early HIV infection is considered a period of high infectivity,[42] and early ART substantially reduces the risk of HIV transmission.[43-46]

Drug-Resistance Testing in the Setting of Early HIV Infection

Prior to the widespread use of INSTIs, data from the United States and Europe demonstrated that transmitted virus strains with resistance to at least one ARV drug were present in up to 16% of people with HIV.[47,48] In one study, 21% of isolates from people with acute HIV infection demonstrated resistance to at least one ARV drug, most commonly non-nucleoside reverse transcriptase inhibitors (NNRTIs).[49-51] The rate of transmitted INSTI resistance was reported to be ≤2.5% of the samples tested, and <0.5% with second-generation INSTIs.[52-55] Before initiating ART in a person with early HIV infection, a blood specimen should be sent for standard genotypic drug-resistance testing for mutations in the reverse transcriptase and protease genes **(AIII).** Genotype testing for INSTI resistance should be performed for those who acquire HIV during or after the use of CAB-LA as PrEP, if transmitted INSTI resistance is suspected, or if HIV diagnosis occurs after receiving an INSTI-based regimen for post-exposure prophylaxis (PEP) **(AIII).**[22]

Treatment should not be delayed pending resistance-test results. The test results should be used to modify the ARV regimen if necessary **(AII).** In people with no history of CAB-LA use or use of an INSTI-based regimen for PEP, the Panel on Antiretroviral Guidelines for Adults and Adolescents does not currently recommend genotype testing for INSTI resistance given the low rate of transmitted INSTI resistance and the high barrier to resistance of bictegravir (BIC) and dolutegravir (DTG), unless transmitted INSTI resistance is a concern **(AIII).**

Considerations for Preventing HIV Transmission During Early HIV Infection

People with early HIV infection have a higher likelihood of sexual transmission of HIV to others. Prompt initiation of ART and sustained viral suppression to <200 copies/mL can prevent transmission of HIV to sexual partners. Individuals starting ART should use another form of prevention (e.g., condoms, PrEP for partners who are HIV negative, sexual abstinence) for at least the first 6 months of treatment and until they have a documented viral load of <200 copies/mL **(AII).** Many experts would recommend confirming sustained viral suppression before assuming no risk of sexual transmission of HIV **(AIII)** (see Antiretroviral Therapy to Prevent Sexual Transmission of HIV).

Antiretroviral Regimens for Early HIV Infection

ART should be initiated with one of the combination regimens recommended for people with chronic HIV infection **(AIII)** (see What to Start). Providers should inform individuals starting ART of the importance of adherence in achieving and maintaining viral suppression **(AIII).** If available, the results of ARV drug-resistance testing or the resistance pattern of the source person's virus should be used to guide selection of the regimen. All people of childbearing potential should undergo a pregnancy test before initiating ART **(AIII).**

For individuals who have not received CAB-LA as PrEP prior to diagnosis of acute HIV, one of the following INSTI-based regimens is recommended **(AIII):**

- BIC/TAF/FTC
- DTG with (TDF or TAF) plus (3TC or FTC)

DTG and BIC are good treatment options because transmitted resistance to second-generation INSTIs in the United States is rare at present and both BIC and DTG have a high barrier to resistance.

For individuals who acquire HIV during and after the use of CAB-LA as PrEP:

- While awaiting integrase genotype results, the use of an INSTI-based regimen **is not recommended (AIII).** The recommended regimen, until resistance testing confirms the absence of INSTI-resistance mutations, is a cobicistat (COBI)- or ritonavir (RTV)-boosted darunavir (DRV) with (TAF or TDF) plus (FTC or 3TC) **(AIII).**

A pharmacologically boosted protease inhibitor (PI)–based regimen (e.g., boosted DRV) is an option because resistance to PIs emerges slowly, and clinically significant transmitted resistance to PIs is uncommon. Therefore, boosted DRV plus (TAF or TDF) plus (FTC or 3TC) is generally recommended in this setting. Baseline laboratory testing recommended for individuals with chronic HIV infection should be performed (see Laboratory Testing for Initial Assessment and Monitoring of People With HIV Receiving Antiretroviral Therapy). Individuals with hepatitis B virus/HIV coinfection should receive TDF/FTC or TAF/FTC as part of their ARV regimen.

Given the increasing use of TDF/FTC[56-58] and TAF/FTC as PrEP,[59,60] early HIV infection may be diagnosed in some people while they are taking TDF/FTC or TAF/FTC. In this setting, drug-resistance test results are particularly important; however, these regimens remain reasonable treatment options pending drug-resistance test results.

Abacavir/3TC **is not recommended** for treatment of acute HIV infection unless the person is known to be HLA-B*5701-negative, and this information is rarely available in people with acute HIV infection. Additionally, due to relatively high rates of transmitted drug resistance for NNRTIs, agents in this drug class **are not recommended** as a component in the regimen of people initiating ART before the results of drug-resistance tests are available.

Treatment Regimens for Early HIV Infection During Pregnancy

All people of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII).** Because early HIV infection, especially in the setting of high-level viremia, is associated with a high risk of perinatal transmission, all pregnant people with HIV should start combination ART as soon as possible to prevent perinatal transmission **(AI).** COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been reported during the second and third trimesters. For more information on the safety and efficacy of ARV use in pregnancy, refer to the Perinatal Guidelines.

Follow-Up After Antiretroviral Therapy Initiation

After ART initiation, monitoring of plasma HIV RNA levels, CD4 T lymphocyte cell counts, and adverse effects should be performed as described in Laboratory Testing for Initial Assessment and Monitoring of People With HIV Receiving Antiretroviral Therapy (i.e., HIV RNA testing 2–8 weeks after ART initiation, then every 4–8 weeks until viral suppression and every 3–4 months thereafter) **(AII).**

Table 14. Identifying, Diagnosing, and Treating Acute and Recent HIV Infection

Suspicion of Acute HIV Infection

- Health care providers should consider the possibility of acute HIV infection in people with the signs, symptoms, or laboratory findings described below and in asymptomatic people with a possible acute (within 2–6 weeks) exposure to HIV.[a]
  - Signs, symptoms, or laboratory findings of acute HIV infection may include but are not limited to, one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, pharyngitis, oral ulcers, leucopenia, thrombocytopenia, and transaminase elevation.
  - High-risk exposures include sexual contact with someone who has HIV or is at risk of HIV infection, sharing needles, syringes, or equipment for drug preparation or injection, or any situation where a person's mucous membranes or broken skin come into contact with bodily fluids that may carry HIV.

Differential Diagnosis

- The differential diagnosis of acute HIV infection may include but is not limited to, viral illnesses such as COVID-19, EBV and non-EBV (e.g., CMV) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis. Diagnosis of any STI should prompt HIV testing and consideration of acute HIV infection.

Testing to Diagnose or Confirm Acute HIV Infection

- Acute HIV infection is defined as detectable HIV RNA or p24 antigen (the specific antigen used in currently available HIV-1/2 Ag/Ab combination assays) in the setting of a negative or indeterminate HIV antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV infection is suspected requires plasma HIV RNA testing to diagnose acute HIV infection.
- A positive result on a quantitative or qualitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. In this case, the diagnosis of HIV infection should be confirmed by subsequent documentation of HIV antibody seroconversion.
- A positive HIV Ag/Ab test result or a positive HIV RNA test result in the setting of a negative HIV antibody test result in a person taking PrEP should prompt immediate confirmation of HIV diagnosis. It is important to collect a new blood specimen to verify the HIV diagnosis before initiating HIV treatment.

Antiretroviral Therapy After Diagnosis of Early HIV Infection

- ART is recommended for all people with HIV, including those with early HIV infection **(AI).** ART should be initiated as soon as possible after HIV diagnosis **(AII).**
- Once initiated, the goals of ART are to achieve sustained plasma virologic suppression, prevent HIV transmission **(AII),** and preserve immune function **(AIII).**
- All people of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII).**
- Pregnant people with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV **(AI).**
- A blood sample for genotypic drug-resistance testing should be obtained before initiating ART to guide the selection of the regimen **(AIII),** but ART should be initiated as soon as possible, often before resistance-test results are available. If resistance is subsequently identified, treatment should be modified as needed.

Table 14. Identifying, Diagnosing, and Treating Acute and Recent HIV Infection

- Standard genotypic drug-resistance testing should be performed for mutations in the reverse transcriptase and protease genes **(AIII)** for all people with early HIV**.** Genotype testing for INSTI resistance should be performed for those who acquire HIV during or after the use of CAB-LA as PrEP, if transmitted INSTI resistance is suspected, or if HIV diagnosis is made after receiving an INSTI-based regimen for PEP **(AIII).**
- ART can be initiated before the results of drug-resistance testing are known. For individuals who do not have a history of using CAB-LA as PrEP, one of the following ARV regimens is recommended **(AIII):**
  - BIC/TAF/FTC **(AIII**); or
  - DTG with (TAF or TDF)[b] plus (FTC or 3TC) **(AIII)**
- For individuals with a history of using CAB-LA as PrEP, genotypic resistance testing performed before starting ART should include screening for INSTI-resistance mutations **(AIII).** Recommended regimens include the following:
  - (DRV/c[c] or DRV/r) with (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype **(AIII).** Empiric INSTI-containing regimens **are not recommended (AIII),** because INSTI resistance may be present in those who acquire HIV during the use of CAB-LA and possibly up to 4 years after.

[a] In some settings, activities that increase the risk of HIV infection may not be recognized or perceived as risky by the health care provider, the person at risk, or both. Thus, even in the absence of reported high-risk activities, symptoms and signs consistent with acute retroviral syndrome should motivate health care providers to consider a diagnosis of acute HIV infection.

[b] TAF and TDF are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

[c] COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been reported during the second and third trimesters.

Key: 3TC = lamivudine; Ag/Ab = antigen/antibody; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CAB-LA = long-acting cabotegravir; CMV = cytomegalovirus; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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HIV-2 Infection

Updated: December 06, 2023
Reviewed: December 06, 2023

Key Considerations and Recommendations
• The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and lower mortality rate than HIV-1 infection. However, without treatment, the majority of individuals with HIV-2 will progress to AIDS and death.
• No randomized controlled trials have addressed when a person with HIV-2 should start antiretroviral therapy (ART) or which regimens are most effective for initial or second-line ART when treating HIV-2; thus, the optimal treatment strategy is not well defined.
• Existing data on the treatment of HIV-2, and extrapolation from data on the treatment of HIV-1, suggest that ART should be started at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others **(AIII).**
• Quantitative plasma HIV-2 RNA viral load testing for clinical care is available and should be performed before initiating ART **(AIII).**
• For ART-naive patients who have HIV-2 mono-infection or HIV-1/HIV-2 coinfection, antiretroviral (ARV) regimens should include an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs) **(AII).** A recommended alternative regimen is a boosted protease inhibitor (PI) that is active against HIV-2 (darunavir or lopinavir) plus two NRTIs **(BII).**
• HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs); therefore, NNRTI-based regimens, including long-acting injectable rilpivirine (given with the INSTI cabotegravir), **are not recommended** for treatment of HIV-2 **(AIII).**
• Patients with hepatitis B virus (HBV)/HIV-2 coinfection should be prescribed ART that contains drugs with activity against both HIV-2 and HBV **(AIII).**
• HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be used to assess treatment response **(AII).** Unlike people with HIV-1, people with HIV-2 should continue to undergo periodic CD4 testing even if their viral loads are persistently suppressed, because disease progression can occur despite an undetectable viral load **(AIII).**
• Resistance-associated viral mutations to INSTIs, PIs, or NRTIs may develop in people with HIV-2 while they are on ART. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are approved for clinical use.
• In the event of virologic, immunologic, or clinical failure, a new ARV regimen should be constructed in consultation with an expert in HIV-2 management.
• *In vitro* studies demonstrate that HIV-2 is intrinsically resistant to the fusion inhibitor enfuvirtide, and limited data also show that HIV-2 is intrinsically resistant to fostemsavir); therefore, these drugs **are not recommended** for treatment of people with HIV-2 **(AIII).**
• For patients with multidrug-resistant virus, ibalizumab and lenacapavir demonstrate *in vitro* potency against HIV-2 and may be considered **(BIII).**
***Rating of Recommendations**: A = Strong; B = Moderate; C = Weak*
***Rating of Evidence**: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Overview

HIV-2 infection is endemic in West Africa, with certain countries experiencing a population prevalence of >1%. The possibility of HIV-2 infection should be considered when treating people of

West African origin, people who have had sexual contact with or shared needles with people of West African origin, and people who reside in countries with strong socioeconomic ties to West Africa (e.g., France, Spain, Portugal, and former Portuguese colonies, such as Brazil, Angola, Mozambique, and parts of India). Globally, it has been estimated that 1 million to 2 million people have HIV-2—a number that includes people with HIV-1/HIV-2 dual infection. However, current and accurate prevalence data are scarce, and neither the Joint United Nations Programme on HIV and AIDS nor the World Health Organization has formal surveillance systems for HIV-2.[1]

Clinical Course of HIV-2 Infection

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and a lower mortality rate than HIV-1 infection.[2,3] However, without effective antiretroviral therapy (ART), HIV-2 infection will progress to AIDS and death in the majority of individuals.[4] Concomitant infection with HIV-1 and HIV-2 may occur, and the possibility of this coinfection should be considered when treating people from areas with a high prevalence of HIV-2.

Diagnostic and Monitoring Assays for HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in people who have clinical conditions that suggest HIV infection but who have atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot).[5] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in people who have serologically confirmed HIV infection but low or undetectable HIV-1 RNA levels, or in those who have declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on ART.

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing[6] recommend using an HIV-1/HIV-2 antigen/antibody combination immunoassay for initial testing and using an HIV-1/HIV-2 antibody differentiation immunoassay for subsequent testing. The Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories) is approved by the U.S. Food and Drug Administration (FDA) to differentiate HIV-1 infection from HIV-2 infection. The Multispot HIV-1/HIV-2 Rapid Test is no longer available. Commercially available HIV-1 RNA assays do not reliably detect or quantify HIV-2 RNA.[7] Quantitative HIV-2 RNA testing is available at the University of Washington (UW)[8] and the New York State Department of Health (NYSDOH).[9] HIV-2 nucleic acid amplification test–based (total DNA/RNA) diagnostic testing is available for clinical care at UW.[10] However, it is important to note that up to one-third of people with untreated HIV-2 will have HIV-2 RNA levels below the limits of detection (10 copies/mL for UW testing and 7 IU/mL for NYSDOH testing); some of these people will have clinical progression and CD4 count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are approved by the FDA for clinical use. HIV-2 genotypic ARV resistance assays are available at UW for research use only.

Treatment of HIV-2 Infection

To date, no randomized controlled trials that address when to start ART or the choice of initial or subsequent ART for HIV-2 have been reported[11]; thus, the optimal treatment strategy has not been defined. Existing data on the treatment of HIV-2 and extrapolation from data on the treatment of HIV-1 suggest that ART should be started at or soon after HIV-2 diagnosis to prevent disease

progression and transmission of HIV-2 to others **(AIII).** However, CD4 cell recovery in people with HIV-2 who are on ART is generally poorer than that observed in people with HIV-1.[12,13]

Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs); however, HIV-2 is more likely to develop resistance to NRTIs than HIV-1.[14] HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs)[15]; thus, NNRTI-based regimens, including the long-acting injectable rilpivirine (RPV) (given with the integrase strand transfer inhibitor [INSTI] cabotegravir [CAB]), **are not recommended** for treatment of HIV-2 **(AIII).** Several small studies in individuals with HIV-2 have reported poor responses to dual-NRTI regimens[16,17] or regimens that contain an NNRTI plus two NRTIs.[18,19] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[20,21]

INSTI-based regimens or protease inhibitor (PI)–based regimens are treatment options for people with HIV-2. As discussed below, three single-arm clinical trials showed favorable outcomes in patients who received INSTI-based regimens. Data regarding the efficacy of PI-based regimens primarily come from observational reports. A randomized controlled trial comparing raltegravir (RAL) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to lopinavir/ritonavir (LPV/r) plus TDF/FTC is completed, but the results have not been reported (FIT-2; NCT02150993).

Integrase Strand Transfer Inhibitor–Based Regimens

All FDA-approved INSTIs—RAL, elvitegravir (EVG), dolutegravir (DTG), bictegravir, and CAB—have potent activity against HIV-2 *in vitro*.[22-27] INSTI-based regimens have shown favorable treatment responses in observational studies.[28-30] Three small, single-arm, open-label clinical trials have assessed the effectiveness of INSTI-based regimens in ART-naive individuals with HIV-2. These studies evaluated RAL plus TDF/FTC, EVG/cobicistat/TDF/FTC, and DTG plus either abacavir/lamivudine or TDF/FTC. All the studies demonstrated favorable clinical and immuno-virologic results at 48 weeks, providing the best evidence to date for HIV-2 treatment recommendations.[31-33]

Protease Inhibitor–Based Regimens

In general, regimens that contain boosted PIs that are active against HIV-2 (and that also include two NRTIs) have resulted in more favorable virologic and immunologic responses than regimens that consist of only two or three NRTIs.[12,13,21,34] Darunavir (DRV), lopinavir (LPV), and saquinavir are more active against HIV-2 than other approved PIs.[35-37] While LPV/r is more active against HIV-2 than DRV *in vitro*, it is less well tolerated. Some clinicians may use boosted DRV (where available) to enhance adherence. Older unboosted PI-based regimens, including nelfinavir or indinavir plus zidovudine and lamivudine, and atazanavir-based regimens have shown poor clinical success rates.[11,16,17,38,39]

Other Antiretroviral Drugs

Among the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.[40] The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates[41]; however, there are no FDA-approved assays that can determine HIV-2 co-receptor tropism, and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[42] The post-attachment inhibitor ibalizumab (IBA) has

potent *in vitro* activity against HIV-2 isolates.[43] Limited data suggest HIV-2 is intrinsically resistant to the attachment inhibitor fostemsavir (FTR).[44,45]

The capsid inhibitor lenacapavir (LEN) demonstrates nanomolar potency against HIV-2 *in vitro* but is 11- to 25-fold less active against HIV-2 than HIV-1.[46,47]

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection[48-51]; however, there are currently no comparative randomized controlled clinical trial data that support the effectiveness of a specific recommended regimen.

The Panel's Recommendations

Until more definitive data on outcomes are available, the Panel on Antiretroviral Guidelines for Adults and Adolescents provides the following recommendations for the management of individuals with HIV-2 mono-infection or HIV-1/HIV-2 dual infection:

- A regimen that contains one INSTI plus two NRTIs is the recommended initial ART for most individuals with HIV-2 **(AII).**
- An alternative regimen is a boosted PI (DRV or LPV) that is active against HIV-2 plus two NRTIs **(BII).**
- HIV-2 is intrinsically resistant to NNRTIs; therefore, NNRTI-based regimens, including long-acting injectable RPV (given with the INSTI CAB), **are not recommended** for treatment of HIV-2 **(AIII).**
- HIV-2 demonstrates intrinsic resistance to the fusion inhibitor enfuvirtide *in vitro*, and limited data show intrinsic resistance to FTR; therefore, these drugs **are not recommended** for treatment of people with HIV-2 **(AIII).**
- For people with multidrug-resistant HIV-2, IBA and LEN may be considered based on *in vitro* data **(BIII).**
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection require ART that contains drugs with activity against both HIV-2 and HBV **(AIII).** See Hepatitis B Virus/HIV Coinfection for more information.
- HIV-2 plasma RNA levels, CD4 counts, and clinical status should be monitored to assess treatment response, as is recommended for HIV-1 **(AII).**
- People who have HIV-2 RNA levels that are below the limits of detection before they initiate ART should still undergo routine HIV-2 plasma RNA monitoring in addition to CD4 count and clinical monitoring. Unlike HIV-1, people with HIV-2 require continued CD4 count monitoring, as disease progression can occur in the setting of undetectable HIV-2 viral load **(AIII).**

People with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as people of childbearing potential with HIV-1 (see What to Start). There are no data on HIV-2 treatment as prevention; however, both data from studies of people with HIV-1 and data on the natural history of HIV-2 transmission suggest that effective ART likely provides a reduced risk of transmission to sexual partners.[52-54]

Viral mutations that are associated with resistance to NRTIs, PIs, and/or INSTIs may develop in people with HIV-2 while they are on ART.[37,55,56] Currently, transmitted drug resistance appears to be rare among people with HIV-2.[57,58] In several small studies, twice-daily dosing of DTG was found to have some residual activity as a second-line INSTI in some people with HIV-2 who had extensive ART experience and RAL resistance.[59-62] Genotypic algorithms that are used to predict drug resistance in HIV-1 may not be applicable to HIV-2 because the pathways and mutational patterns that lead to resistance may differ between the HIV types (see the HIV2EU Algorithm and the Stanford University HIV Drug Resistance Database).[63] In the event of virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.

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HIV and the Older Person

Updated: September 12, 2024
Reviewed: September 12, 2024

Key Considerations and Recommendations When Caring for Older People With HIV
• Diagnosis of HIV at a later stage of disease is more common among older people. Early diagnosis and treatment of HIV and counseling to prevent secondary HIV transmission remain important in the clinical care of older people with HIV. • Antiretroviral therapy (ART) is recommended for all people with HIV **(AI).** ART is especially important for older individuals because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART. • Compared to people without HIV, people with HIV have a twofold higher risk of developing atherosclerotic cardiovascular disease (ASCVD), and their age at incident ASCVD diagnosis is about a decade younger. In addition to current American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guidelines, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends initiating at least a moderate-intensity statin in people with HIV aged 40 to 75 years who have 10-year ASCVD risk estimates of 5% to <20% **(AI).** See Statin Therapy in People With HIV for the Panel's additional recommendations on the use of statin therapy as primary prevention for people with HIV. • Polypharmacy is common in older people with HIV, and all drugs, supplements, and herbal treatments should be assessed regularly for appropriateness, potential for adverse effects, proper dosing, and drug interactions **(AIII).** • Potential for drug–drug interactions between antiretroviral drugs and concomitant medications (including statins, supplements, and herbal medicines) should be assessed regularly, especially before a new ART regimen or concomitant medication is started. In this context, it is also important to inquire and counsel about the use of non-daily medications, including long-acting injectables and as-needed medications. • Adverse drug events from ART and concomitant drugs may occur more frequently in older people with HIV than in younger individuals with HIV. Therefore, the bone, kidney, metabolic, cardiovascular, cognitive, and liver health of older individuals with HIV should be monitored closely. • HIV infection is associated with immunologic aging and systemic inflammation, which may contribute to the development of comorbidities across multiple organ systems as well as aging phenotypes like frailty. HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older people with HIV, including adhering to treatment and prevention guidelines for different medical comorbidities. • Age-related decline in neurocognitive function is faster in people with HIV compared to those without. Cognitive impairment in people with HIV—with manifestations including problems with memory, attention, and executive function—is associated with reduced adherence to therapy and poorer health outcomes, including increased risk of death. For people with progressive cognitive impairment, referral to a specialist (e.g., neurologist, neuropsychologist, geriatrician) for evaluation, testing, and management may be warranted **(BIII).** • Mental health disorders, including an increased risk of anxiety and depression, are a concern among aging people with HIV. Screening for depression and management of mental health issues are important when caring for older people with HIV. • Given that the burden of aging-related diseases is significantly higher among people with HIV than in the general population, additional medical and social services may be required to effectively manage both HIV and comorbid conditions.
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Effective antiretroviral therapy (ART) has increased survival in people with HIV[1-4], resulting in an increasing number of older people with HIV. In the United States in 2022, the proportion of people newly diagnosed with HIV aged ≥55 years was 9%, according to the Centers for Disease Control and Prevention (CDC). Among people with HIV in 2022, 38% were aged ≥55 years, 13.2% were aged ≥65 years, and these proportions are expected to increase steadily.[5] The difference in life expectancy between people with HIV and the general population has significantly narrowed since the use of effective ART and is now estimated to be 5 years or fewer for those with CD4 T lymphocyte (CD4) cell count >500/µL after initiating ART.[3] However, the difference in mortality rates increases significantly with advancing age. While there has been a large reduction in AIDS-related mortality with effective ART, noninfectious comorbidities and complications, including atherosclerotic cardiovascular diseases (ASCVD) and non-AIDS malignancies, now account for a growing proportion of the causes of death among people with HIV.[2,3,6,7]

The discussion in this section of the guidelines refers to individuals aged ≥50 years as older people with HIV. Many older people with HIV have had HIV for years or decades; therefore, accumulating disease risk associated with longstanding HIV disease itself and/or exposure to antiretroviral (ARV) medications (including prior use of older ART regimens with greater toxicity in some cases) should be considered. Specifically, HIV may affect the biology of aging, possibly resulting in earlier manifestations of morbidities generally associated with more advanced age. As a result, older people with HIV may suffer from aging-related illnesses earlier and at higher rates than those without HIV, and will require more non-ART medications than younger people, which may complicate HIV clinical care.[8,9,10]

It is also important to consider distinct issues for people who are diagnosed with and/or acquire HIV at older ages. For example, older adults may have an increased risk of acquisition and transmission of HIV, in part as a consequence of reduced mucosal and immunologic defenses and changes in risk related-behaviors (e.g., decrease in condom use because of less concern about pregnancy or more high-risk sexual activity with increased use of erectile dysfunction drugs).[11,12] In addition, HIV screening among older adults remains low because they are generally perceived to be at low risk of acquiring HIV. The sections below review important considerations for the diagnosis and treatment of HIV among older people, as well as the potential clinical implications for people now living to older ages with longstanding HIV disease.

HIV Screening and Diagnosis in the Older Person

Older people with HIV (aged ≥55 years) are significantly more likely to meet the case definition of AIDS at HIV diagnosis than people aged <55 years (threshold defined by CDC surveillance data).[13] Also, older adults appear to have lower CD4 counts at seroconversion and steeper CD4 count decline over time[14] and tend to present to care with significantly lower CD4 counts.[15,16] Therefore, education, preventive measures (including pre-exposure prophylaxis or PrEP), and routine screening of asymptomatic older adults for HIV should be emphasized,[17] as well as considering HIV infection in the medical evaluation of older adults.

Antiretroviral Therapy in the Older Person With HIV

Importance of Prompt Initiation of Antiretroviral Therapy After HIV Diagnosis

ART is recommended for all individuals with HIV (**AI;** see Initiation of Antiretroviral Therapy). Early treatment may be particularly important in older adults because of blunted immune recovery and increased risk of serious non-AIDS events in this population.[18,19] However, ART-associated CD4 cell recovery in older adults is generally slower and lower in magnitude than in younger people,[20-23] suggesting that early diagnosis and treatment may result in better immunologic response and possibly improved clinical outcomes. In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (people aged 45 to 65 years).[24] The benefits of early ART initiation were further demonstrated in an analysis of HIV cohorts from Europe and the Americas showing a lower all-cause and non-AIDS mortality with immediate ART initiation in people aged 50 to 70 years.[25] More definitive information was provided by the START study, which randomized ARV treatment–naive participants with CD4 counts >500 cells/mm^3 to either immediate ART or deferred ART until CD4 count dropped below 350 cells/mm^3. The highest absolute risk reduction of serious AIDS and non-AIDS events associated with immediate ART was found in participants aged 50 years or older.[26] All older people with HIV should be informed that maintaining a plasma HIV RNA (viral load) at <200 copies/mL with ART improves overall health and prevents sexual transmission of HIV (see the Treatment as Prevention section).

Choice of Antiretroviral Regimens in the Older Person With HIV

The choice of ARV regimen for an older person with HIV should be informed by a comprehensive review of the person's other medical conditions and medications (including non-prescription drugs, supplements, and herbal treatments), and results from cumulative genotypic resistance testing. The What to Start section (Table 7) of these guidelines provides guidance on selecting an ARV regimen based on a person's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease [CVD], osteoporosis). In older people with HIV and reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix B, Table 12). In addition, ARV regimen selection may be influenced by potential interactions between ARV medications and drugs used concomitantly to manage comorbidities (see Tables 24a through 25b). Adults aged >50 years should be monitored for ART effectiveness and safety as similarly recommended for other populations with HIV (see Table 3); however, in older people, special attention should be paid to the greater potential for adverse effects of ART on renal, liver, cardiovascular, central nervous system, metabolic, and bone health (see Table 20). A meta-analysis confirmed that people with HIV have a 1.5-fold higher risk of fragility-related fracture and a fourfold higher risk of hip fracture. The increased risk is not completely explained by differences in bone mineral density (BMD) alone, indicating there may be differences due to bone microarchitecture or other HIV-related factors contributing to the marked fracture risk. ART regimens that contain tenofovir disoproxil fumarate (TDF),[27] boosted protease inhibitors (PIs), or both are associated with a significantly greater loss of BMD, with or without osteoporosis, compared to regimens containing other NRTIs and integrase strand transfer inhibitors (INSTIs).[28-31] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide (TAF) may be considered as alternatives to the use of TDF in older individuals who may be at risk of nephrotoxicity, osteopenia, or osteoporosis; however, with ABC, the benefit should be balanced with its potential for increasing the risk of CVD (see What to Start). The long-acting (LA) injectable combination of cabotegravir (CAB) and rilpivirine (RPV) is also an option for ART among older people with HIV, with the same

considerations as for all people with HIV (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).

Antiretroviral Efficacy and Safety Considerations in the Older Person With HIV

The efficacy, pharmacokinetics (PK), adverse effects, and drug interaction potentials of ART in older adults have not been studied systematically. Data from clinical trials of second-generation INSTIs (dolutegravir [DTG] and bictegravir),[32] two-drug regimens (DTG/lamivudine),[33] and LA CAB/RPV have shown similar virologic efficacy, safety, and tolerability between participants >50 years of age and those aged 50 and younger.[34]

Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of ARV drugs. Both liver and kidney functions decrease with age and may result in impaired drug elimination and increased drug exposure.[35] Most clinical trials have included only a small proportion of participants aged >50 years, and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function. Because it is not known whether drug accumulation in older people may lead to greater incidence and severity of adverse effects than in younger people, therapy in older people requires close monitoring and heightened awareness of drug-related adverse effects, especially in those with hepatic or renal impairment.

Adherence Concerns

Suboptimal adherence to ART is the most common cause of treatment failure. Although most older people with HIV are able to achieve viral suppression with a single-tablet regimen, some people who have a long history of ART may have acquired drug resistance, thus requiring more complex multiple-pill regimens. Complex dosing requirements, high pill burden, polypharmacy, inability to access medications because of cost or availability, limited health literacy (including misunderstanding of instructions), depression, substance use, frailty, and neurocognitive impairment are among the key reasons for nonadherence and should be regularly assessed and managed (see Adherence to the Continuum of Care).[36-38] Although some of the factors associated with nonadherence may be more prevalent in older people with HIV, older people have demonstrated better adherence to ART than younger people in some studies.[39-41] Severe menopausal symptoms are also associated with reduced adherence to ART, which increases the risk of drug resistance and adverse HIV-related health outcomes in menopausal cisgender women, highlighting the importance of managing these symptoms among women with HIV.[42,43] To facilitate ART adherence, it may be useful to discontinue unnecessary non-HIV medications, simplify ART regimens, and apply evidence-based behavioral approaches including the use of adherence aids such as pillboxes or daily calendars, and support from family members and friends (see Adherence to the Continuum of Care). LA dosing options, such as LA CAB/RPV, may ease pill burden and adherence concerns for some older adults (see Optimizing Antiretroviral Therapy).

Optimizing Antiretroviral Therapy in Older People With HIV

Given the greater incidence of comorbidities, non-AIDS complications, and frailty among older people with HIV, switching one or more ARVs in an HIV regimen may be necessary to minimize toxicities, drug–drug interactions, or to reduce pill burden.[38] Expert guidance now recommends bone density monitoring in men aged ≥50 years and postmenopausal cisgender women and suggests switching from TDF or boosted PIs to other ARVs (such as TAF or INSTIs, respectively) in older

people at high risk for fragility fractures.[44] Given the high prevalence and faster progression of chronic kidney disease (CKD) in aging people with HIV—likely from a combination of HIV, ART, and non-HIV risk factors—development of CKD must be closely monitored in an older person on ART.[45,46] Table 7 provides guidance for ARV drugs to use based on selected clinical scenarios, including comorbidities.

Polypharmacy in Older People With HIV

People with HIV and aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management.[8] In addition to taking medications to manage HIV and comorbid conditions, many older people with HIV are also taking medications to relieve discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). Older individuals may also self-medicate with over-the-counter medicines or supplements.

Polypharmacy is more common in older people with HIV than similarly aged people in the general population.[8,47,48] Among people with HIV aged ≥65 years, it is predicted that the prevalence of comorbidities and polypharmacy rose with increasing age and duration of HIV infection.[49,50] In the Swiss HIV Cohort Study, the prevalence of polypharmacy and inappropriate prescribing in people aged ≥75 was 66% and 67%, respectively.[51]

In people aging with HIV, the effects of polypharmacy, including the use of drugs that affect neurocognitive function, can contribute to serious adverse outcomes, such as serious falls and fractures, delirium, hospitalization (including intensive care unit admissions), and death.[52-57] Polypharmacy may also increase the likelihood of adverse consequences such as medication errors (by prescribers or prescription recipients), medication nonadherence, additive drug toxicities, and drug–drug interactions. Older people with HIV are probably at an even greater risk of polypharmacy-related adverse consequences than younger or similarly aged people without HIV. When evaluating any new clinical concern or laboratory abnormality in people with HIV, especially in older people, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

Drug–Drug Interaction Concerns

Interactions between ARV drugs and concomitant medications, supplements, and herbal treatments can occur and can be easily overlooked by prescribers.[58] Potential drug–drug interactions can occur between ARV and non-ARV medications, as well as between non-ARV medications.[48,59] The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young participants with normal organ function who do not have HIV (see Tables 24a–25b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of an interaction may be greater in older than in younger people with HIV; therefore, it is important for clinicians to remain vigilant to assess for potential drug–drug interactions given the high prevalence of polypharmacy in older people with HIV. The risk of significant drug–drug interactions appears to be higher with PI-based or non-nucleoside reverse transcriptase inhibitors-based ART than with INSTI-based ART, although there are some important interactions with INSTIs that should be recognized and managed (including with polyvalent cations that are frequently taken as supplements).[60-62]

Hormonal therapies may be taken to alleviate symptoms of menopause among cisgender women or to facilitate gender affirmation among transgender individuals. Although data on drug–drug interactions between hormonal therapies and ART are limited, existing data suggest little to no impact of hormonal therapies on the efficacy of some ART.[63-65]

HIV and Immunologic Aging

Chronic HIV infection is associated with elevated soluble markers of immune activation and inflammation, as well as cellular phenotypes indicative of T cell and myeloid cell activation, even after HIV RNA levels are suppressed with ART.[66] The levels of inflammation and immune activation also increase with age and age-associated diseases.[67] In this context, the combined effects of HIV and advancing age on chronic inflammation have implications for risk from a broad spectrum of diseases.[68,69]

A contributing factor to the early development of aging-related diseases among people with HIV has been posited to be the effect of HIV on immunologic aging. In addition to higher levels of immune activation, aging is associated with a higher frequency of cellular senescence as well as impaired immune responses and surveillance.[70] HIV infection is associated with higher frequencies of T cell phenotypes characteristic of immunosenescence, as well as phenotypes reflective of highly differentiated or activated states.[71-74] Higher frequencies of senescent T cells are then associated with a greater risk for such comorbidities as CVD. In addition, the degree of CD4 T cell recovery after ART initiation is diminished among people ≥50 years old versus younger people with HIV.[75,76] This impaired T cell recovery with advancing age may then have functional consequences, as people with HIV demonstrate reduced immune responses to vaccination, as well as impaired control of copathogens such as cytomegalovirus (CMV).[77-79] The persistence of impaired or ineffective immune response toward copathogens then contributes to ongoing chronic immune activation (e.g., CMV-specific responses),[78] as well as the increased risk of both AIDS and non-AIDS–defining cancers that are driven by pro-oncogenic viruses (e.g., human papillomavirus [HPV]-and Epstein-Barr virus [EBV]-related cancers).[80]

Immunologic aging in the context of HIV also entails chromosomal and genetic changes. Whether a consequence of untreated HIV viremia, direct toxicity from ARV drugs, or both, people with HIV have been shown to have shorter leukocyte chromosome telomere length, itself a marker of poor health and mortality.[81-83] DNA methylation is an epigenetic alteration that occurs at a predictable rate with advancing age, predicts lifespan, and increases in the setting of chronic HIV disease.[84-87] Finally, a genetic mechanism that may more directly link immunologic aging to comorbid disease risk is clonal hematopoiesis, which entails an age-related expansion of somatic gene mutations among leukocytes (also referred to as age-related clonal hematopoiesis or ARCH). Clonal hematopoiesis is more common among people with HIV, and the degree of difference with people without HIV may be more pronounced with advancing age[88,89] and in people with low nadir CD4 counts.[90,91] Several of the leukocyte gene mutations characteristic of clonal hematopoiesis lead to dysregulation of inflammatory pathways, which is then associated with higher levels of inflammatory markers and ASCVD.[92-94] In summary, clonal hematopoiesis is an example of HIV disease influencing age-related genetic somatic mutations that may contribute to ongoing systemic inflammation and associated disease risk among older people with HIV.

Disease-modifying pharmacologic interventions targeting immunologic aging are an area of active study within geroscience, but none are currently recommended specifically for older people with

HIV with the exception of statin therapy as primary prevention of ASCVD risk (see Atherosclerotic Cardiovascular Disease in the Older Person With HIV below and Statin Therapy in People With HIV).

Morbidity, Mortality, and Non-AIDS Complications Among Older People With HIV

The clinical implications of greater immunologic aging and persistent inflammation can manifest in any organ system, diminishing the health span of older people with HIV. The frailty phenotype—defined clinically as a decrease in muscle mass, weight, physical strength, energy, and physical activity—represents an important example of an age-related syndrome that occurs with greater frequency and at earlier ages among people with HIV and is associated with a broad spectrum of adverse effects and disease risk. Specifically, frailty among people with HIV has been associated with incident CVD, diabetes mellitus, recurrent falls and fractures, lower quality of life, cognitive impairment, hospitalization, and mortality.[95-104] The frailty phenotype remains incompletely characterized among older people with HIV and identifying effective treatment strategies is an important priority for clinical management. However, pharmacologic and non-pharmacologic interventions addressing frailty among people with HIV have been proposed and have the potential to significantly impact their quality of life and survival.[105,106]

Although the life expectancy of people with HIV is approaching that of people without HIV, the incidence and prevalence of age-associated comorbidities in people with HIV are increasing.[107,108] The age-related comorbidity burden is significantly higher in people with HIV compared to the age-matched general population.[8] These predictions differ by comorbidity and by demographic factors—including race, ethnicity, age, gender identity, and HIV transmission mode—displaying substantial disparities for some populations.

Data from insured adults suggest that people with HIV spend approximately 15 years more of their lifespan with one or more major comorbidities when compared to people without HIV; this difference is reduced but persists (at approximately 10 years) for people who initiate ART at a CD4 count of >500 cells/mm^3.[109] A simulation modeling study projected that by 2030, 45% of people with HIV on ART would be living with two or more physical comorbidities and 64% with at least one mental health comorbidity.[110]

Non-AIDS–Defining Complications and Comorbidities in the Older Person With HIV

Non-AIDS comorbid conditions constitute an increasing proportion of morbidity and mortality among people with HIV.[3,111] Heart disease and cancer are the leading causes of death in older people with HIV in the United States. Similarly, other non-AIDS events, such as cognitive impairment and liver disease, have also emerged as major causes of morbidity and mortality in people with HIV receiving effective ART. The prevalence of multimorbidity among people with HIV has increased in the past decade,[112] with hypertension and hypercholesterolemia being the most common comorbidities.[113]

Three groups of factors likely contribute to this burden of noncommunicable diseases among people with HIV: (1) an over-representation of traditional risk factors in this population, especially higher rates of smoking, diabetes, and dyslipidemia; (2) HIV-associated chronic inflammation and immune activation, which are not completely abated by suppressive ART; and (3) possible cardiometabolic complications of some ARV drugs.[114-122]

As the life expectancy of people with HIV increases with ART, more cisgender women with HIV are experiencing menopause. Although menopause may occur earlier in cisgender women with HIV than in cisgender women in the general population,[123] early menopause may also be a consequence of smoking, depression, substance use disorder, and other psychosocial factors that are disproportionately present in cisgender women with HIV.[124] Also, HIV might compound menopause-related metabolic changes. For instance, HIV infection and menopausal stage were independent predictors of lower BMD and had an additive effect on lumbar spine and total hip BMD.[125]

HIV-specific primary care guidelines have been developed and are available for clinicians caring for people with HIV, especially for older people with HIV.[126,127] Additional specific guidelines have also been developed for the evaluation and management of the following specific comorbidities in people with HIV: bone health,[44] kidney disease,[128] and secondary prevention for ASCVD.[129] In addition, the following guidelines recently developed for the general population can be applied to older people with HIV: management of hypertension[130], hyperglycemia[131], and hyperlipidemia.[132] However, it is important to note that the recommendations in many of these guidelines have not all been validated in the context of HIV disease. For instance, cardiovascular risk prediction functions developed for the general population likely underestimate the risk in people with HIV.[129,133] Findings of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study have provided significant insight into the potential role of statins in the prevention of major adverse cardiovascular events in people with HIV. See Statin Therapy in People With HIV for recommendations from the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) on statin therapy as primary prevention of ASCVD among people with HIV. Further analyses of the REPRIEVE data will likely yield additional insights into their benefits (and potential risks) in people with HIV, as well as differences in the predictive value of risk equation scores in demographic subsets of study participants.

Atherosclerotic Cardiovascular Disease in the Older Person With HIV

When compared to people without HIV, data from several studies have shown that people with HIV have about a twofold higher risk of developing ASCVD, and their age at incident ASCVD diagnosis is about a decade younger.[108,109,134,135] ASCVD risk prediction tools used for the general population tend to underestimate risk among people with HIV.[133,136] Data also suggest that the relative increase in ASCVD risk is greater among women with HIV than among age-matched men with HIV when compared to people without HIV.[137,138] Factors influencing ASCVD risk among people with HIV include both higher prevalence of traditional cardiometabolic risk factors and ongoing systemic inflammation associated with HIV,[114,137] even in individuals with viral suppression while on ART. In addition, structural barriers and health disparities in screening and treatment of ASCVD risk factors likely also contribute to excess ASCVD risk among people with HIV in the United States.[139,140]

The 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guidelines provide recommendations on the use of statins as primary prevention based on risk stratification using estimates of 10-year ASCVD risk from the pooled cohort equations.[141,142] In the general population, statin therapy is recommended for all people at high 10-year ASCVD risk (defined as ≥20%). Recent findings from the REPRIEVE trial have provided evidence for the use of statin therapy as primary prevention for people with HIV at low-to-intermediate ASCVD risk (i.e., <20%). REPRIEVE, a large randomized controlled trial among people with HIV aged 40 to 75 years who were receiving ART, showed that when compared to placebo, pitavastatin 4 mg daily was associated with a 35% reduction in major adverse cardiovascular events over a median follow-up duration of 5 years.[143] Results from REPRIEVE informed the Panel's recommendation on the use of

at least moderate-intensity statin therapy as primary prevention among people with HIV of age 40 to 75 years, with a stronger recommendation for those with ASCVD risk score ≥5% who will have a higher absolute benefit from statin therapy. See Statin Therapy in People With HIV for the Panel's full recommendations on statin therapy.

Neurocognitive Impairment in the Older Person With HIV

Cognitive impairment in people with HIV can manifest as difficulty with memory, attention, speed of information processing, and executive and motor functions. Studies that use neuropsychological testing to define categories of impaired cognition—termed HIV-associated neurocognitive disorder (HAND)—find that up to 30% of people with HIV on virally suppressive ART meet these research-based criteria[144], although these categories have not been validated for use in clinical practice. Research studies also demonstrate a steeper decline in performance on neuropsychological tests with advancing age in individuals with HIV compared to those without HIV over the same age range.[145] Although viral persistence and chronic brain inflammation can contribute, cognitive impairment is multifactorial in people with HIV. It is not solely HIV-associated, but also influenced by factors related to comorbidities, including polypharmacy, mood disorders, vascular disease, social isolation, stress, and independent neurodegenerative conditions.[146-151] Hormonal shifts that occur with aging may contribute to neurocognitive impairment, and these changes may manifest as unique differences in clinical manifestations by sex assigned at birth.[152] Finally, the risk of neurodegenerative disease rises with increasing age independent of HIV, and diagnosis of Alzheimer's disease or other forms of progressive dementia in older people with HIV is now an important clinical concern.[153]

Cognitive impairment carries potentially detrimental clinical consequences for aging people with HIV. In a prospective observational study, cognitive impairment was predictive of a lower likelihood of retention in care among older people.[154] Cognitive impairment is also associated with reduced adherence to therapy[155] and poorer health outcomes including increased mortality.[156] Given the importance of cognitive health, screening for neurocognitive impairment is important, though optimal primary care-based screening methods remain unclear. Initial screening with questions about symptoms of memory loss, slowness, and poor attention can help to guide the need for referral to a specialist (e.g., neurologist, neuropsychologist, or geriatrician).[157,158] Though such questions can be useful in identifying cognitive impairment, a positive response to these questions is not necessarily specific to impairment related to HIV.[159] Of note, people with substantial impairment may not have enough insight into their condition to answer the questions, and input from a partner or family member corroborating the impaired person's cognitive history may enhance the validity of the assessment. No brief cognitive screening test has been clearly shown to be sensitive or specific for cognitive impairment in HIV; the frequently used Mini-Mental State Exam does not typically capture executive function impairment, which is the main manifestation of subtle cognitive impairment in people with HIV.[160] The Montreal Cognitive Assessment may be more sensitive but is not specific. A lower threshold than the original cut-off score of 26 on the Montreal Cognitive Assessment is likely more optimal for HAND screening, as it lowers false positive rates and improves diagnostic accuracy.[161] If a person has persistent concerns over time, has symptoms corroborated by an acquaintance, or has progressively worsening symptoms, referral to a neurologist for evaluation and management or to a neuropsychologist for formal neuropsychological testing may be warranted **(BIII).**[160]

Beyond screening and referral to specialists in neurology, neuropsychology, or geriatrics, an approach to cognitive impairment in aging people with HIV should involve assessing and correcting

reversible and treatable factors that contribute to cognitive symptoms, as well as directly addressing modifiable risk factors. Reversible and treatable factors that may contribute to cognitive symptoms include hypothyroidism, low vitamin B12 levels, syphilis, sleep apnea, and cerebrovascular disease.[162] Hearing impairment, diabetes, obesity, hypertension, depression, smoking, alcohol or substance use, and limited physical and social activity have been identified as significant modifiable risk factors for dementia in people without HIV.[163] Given the prevalence of many of these risk factors in older people with HIV, careful attention to their prevention or amelioration is an important component of primary care and cognitive care in aging people with HIV. Finally, the U.S. Preventive Service Task Force now recommends screening older adults (>65 years) for depression.[164]

Mental Health Concerns in the Older Person With HIV

Mental health-related problems are a growing concern in aging people with HIV, though little is known about their prevalence and consequences in this population specifically. In a study that compared a cohort of individuals aged >60 years with HIV to a historical control group of healthy older people, a heightened risk of mood disorders including anxiety and depression was noted among people with HIV.[165] Social isolation combined with depression is particularly common among older adults with HIV and, in addition to its direct effects on morbidity and mortality, it may contribute to poor medication adherence and retention in care.[166,167] The risk of suicide remains greater in people with HIV than in the general population, though increasing age might not further heighten the risk.[168] In one analysis of a multicenter observational study in France, suicide emerged as the second-highest cause of death among virologically suppressed people with HIV on ART.[169] Screening for depression and management of mental health issues are critical aspects of HIV primary care; guidelines for people with HIV, as well as for aging individuals without HIV, recommend behavioral approaches including individual psychotherapy, cognitive behavioral therapy, group therapy, and often pharmacological treatment.[169] When resources are available, integrated care models with routine screening by health care support staff, review by primary providers, and referral to on-site mental health specialists are likely to be the most effective approaches in vulnerable aging populations.

Health Care Utilization and Cost Sharing

The substantially increased burden of age-related comorbidities among people aging with HIV, including CVD, CKD, neurocognitive disease, and fractures, can lead to increased healthcare utilization and higher costs.[170] Out-of-pocket health care expenses (e.g., copayments, deductibles), loss of employment, and other financial-related factors can cause temporary interruptions in treatment, including ART, which should be avoided whenever possible (see Cost Considerations and Antiretroviral Therapy for more information). The increased life expectancy and higher prevalence of chronic complications in aging populations with HIV can place greater demands upon HIV services[171] and require a focused approach to prioritize modifiable health-related problems. Facilitating continued access to health care, including access to insurance-covered care and medications, is essential to minimize treatment interruptions; clinical outcomes can improve with additional multidisciplinary services to manage concomitant chronic disorders and assist with overcoming structural barriers to care. See the Ryan White HIV/AIDS Program's Available Care & Services page for additional information.

End-of-Life Issues, Including Palliative Care and Interruption of ART

As with all aging people, it is important to discuss living wills, advance directives, and long-term care planning. Palliative care and hospice should be discussed with a person-centered approach that

incorporates the person's family situation and cultural, religious, and personal values, among other factors.[172,173]

Few data exist on the use of ART in people with debilitating chronic, severe, or non-AIDS terminal conditions.[174,175] Discontinuation of ART usually results in rebound viremia and a decline in CD4 count; an acute retroviral syndrome has also been reported after abrupt ART discontinuation. For these reasons, most clinicians would continue ART if there are no significant adverse reactions to the ARV drugs. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the affected person and/or family members after a discussion of the risks and benefits of continuing or stopping ART.

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Substance Use Disorders and HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Key Considerations and Recommendations
• Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care **(AII).**
• The most commonly used substances among people with HIV include the following (listed in alphabetical order): alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco.
• Health care providers should be nonjudgmental when addressing substance use with people with HIV **(AIII).**
• People with HIV and SUDs should be screened for additional mental health disorders **(AII).**
• People with HIV and SUDs should be offered evidence-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment; see Table 15 below) as part of comprehensive HIV care in clinical settings **(AI).**
• Ongoing substance use is not a contraindication to antiretroviral therapy (ART). People who use substances can achieve and maintain viral suppression with ART.
• Substance use may increase the likelihood of HIV transmission risk behaviors, the potential for drug–drug interactions, and the risk or severity of substance-associated adverse events (e.g., increased hepatotoxicity or an increased risk of overdose).
• Selection of antiretroviral (ARV) regimens for individuals who practice unhealthy substance and alcohol use should take into account potential adherence barriers, comorbidities that could impact care (e.g., advanced liver disease from alcohol or hepatitis viruses), potential drug–drug interactions, and possible adverse events associated with the medications **(AII).**
• For people with SUDs, ARV regimens with once-daily formulations (ideally as a single-tablet regimen), high barriers to resistance, low hepatotoxicity, and low potential for drug–drug interactions are preferred **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Background on Substance Use Disorders Among People With HIV

Ending the HIV epidemic requires addressing substance use among people with HIV, which poses a barrier to optimal engagement in the HIV care continuum. Ongoing substance use may prevent an individual from being tested for HIV, initiating antiretroviral therapy (ART), or adhering to ART. Substance use may also increase the likelihood of risk-taking behaviors (e.g., sexual transmission risk behaviors, needle sharing, injection of substances), the potential for drug–drug interactions, and the risk or severity of substance-related adverse events (e.g., increased hepatotoxicity and increased risk of overdose). In the United States, the death toll for drug overdose (102,123 deaths as of February 2024)[1] far exceeds the death toll for HIV (4,941 deaths in 2022).[2] As the drug overdose epidemic continues to expand, health care providers need a basic understanding of how to screen for and treat substance use disorders (SUDs) in people with HIV in clinical settings.[3]

Substance use exists on a continuum, from episodic use to an SUD with its concomitant negative consequences. Research on alcohol consumption has defined a threshold at which consumption does not reach a diagnosis of SUD, but where the level of consumption is nonetheless hazardous to the

person. This level of consumption has been defined as at-risk or hazardous use. A comparable category does not exist for other substances. The prevalence of substance use and SUDs is higher among people with HIV than among the general public,[4] and polysubstance use is common. This section will focus on the most commonly used substances among people with HIV (listed in alphabetical order): alcohol, benzodiazepines, cannabinoids, club drugs,[5] opioids, stimulants (cocaine and methamphetamines), and tobacco. Additionally, xylazine, a non-opioid veterinary analgesic that is a common substance adulterant—a substance added to another substance that may lead to negative health consequences—is also discussed.

People with HIV may use more than one substance and may not be ready to consider reducing the use of substances or seeking treatment for SUDs. Polysubstance use occurs for multiple reasons, including to improve the euphoria associated with use (e.g., use of cocaine and heroin mixtures called "speedballs") and to reduce the adverse effects of a particular substance (e.g., the use of alcohol or benzodiazepines to reduce the anxiety caused by cocaine use).

Substance Use and Sexual Risk-Taking

A growing body of literature describes the intersection of substance use and sexual risk-taking, in which drugs are intentionally used to enhance sexual activity ("chemsex"). This research highlights the impact of substance use on sexual transmission risk behaviors; although no precise definition of "chemsex" exists, studies have investigated various substances used to enhance sexual pleasure, decrease inhibitions related to particular sexual acts, and combat low self-esteem. In a retrospective study in a London sexual health clinic, individuals who disclosed substance use (463 of 1,734 participants) had higher odds of acquiring new HIV infection, bacterial sexually transmitted infections (STIs), and/or hepatitis C virus (HCV).[6] A much larger analysis using the European Men Who Have Sex With Men (MSM) Internet Survey, which collected data from 16,065 United Kingdom-based respondents, found that MSM who reported using methamphetamines or gamma-hydroxybutyrate (GHB) during the previous year were more likely to have gonorrhea infection than MSM who did not use these drugs, with odds ratios of 1.92 and 2.23, respectively.[7] Between 2017 and 2020, the American Men's Internet Survey collected data on chemsex drug use among MSM in the United States over the preceding 12 months. Of 30,294 MSM respondents, 3,113 (10.3%) self-reported chemsex in the past 12 months, with 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") (65.1%), methamphetamine (42.5%), and GHB (21.7%) being the top drugs reported for use.[8] A recent study in Spain using an online, self-administered questionnaire found that 81.4% of 2,919 MSM attending four HIV/STI testing sites in Madrid and Barcelona had ever used any drug, and 50% had engaged in chemsex in the past 12 months. Of those engaging in chemsex, half engaged in condomless anal sex.[9] These data emphasize the need to screen people with HIV for substance use and STIs in clinical settings and to discuss strategies with these individuals to reduce potential harm.[10]

Substance Use and Unstable Housing

People with HIV who inject drugs are more likely to be unhoused.[11] Houselessness among people who inject drugs is associated with an increased risk of HIV acquisition.[12]

Among people with HIV and SUD, houselessness confers an increased risk for disruptions in the HIV care continuum independent of ongoing substance use. In a longitudinal study of people with HIV who used drugs, lack of housing was associated with a 44% decrease in the odds of progression through the HIV care continuum.[13] After adjusting for multiple intersecting risks, including

unhealthy alcohol use, other substance use, incarceration, unemployment, education, age, sex, and race/ethnicity, unhoused people with HIV and SUD had significantly decreased odds of ART initiation and, adherence, and of viral suppression.

Interventions supporting housing among people with HIV and SUD can result in improved HIV treatment outcomes. A randomized controlled trial of a rapid rehousing intervention for people with HIV who were houseless (n = 236, 81% with substance use) found that clients in the Enhanced Housing Placement Assistance arm were more likely to be placed and, placed faster, and were twice as likely as the control group to reach or maintain viral suppression (95% confidence interval [CI], 1.1–4.0).[14,15] An observational study of applicants to a supportive housing program for low-income people with HIV and a mental health condition or SUD (n = 958; 86% with SUD) found that people who achieved stable housing were more likely to engage in HIV care and to achieve viral suppression.[16] These data reflect the importance of not only addressing SUD among people with HIV, but also understanding the co-occurring structural determinants that contribute to poorer outcomes among people with HIV and SUD.

Screening for Substance Use Disorders

Screening for SUDs should be incorporated into the routine clinical care of all people with HIV. The following questions can be used to screen for drug or alcohol use: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" and "How many times in the past year have you had X or more drinks in a day?" (X is five for men and four for women).[17] Data are lacking on the appropriate threshold for alcohol use among transgender individuals with HIV, although a study among transgender individuals without HIV recommends a threshold of five standard drinks on a drinking day or a score of ≥3 on the Alcohol Use Disorders Identification Test (AUDIT-C).[18] Individuals with liver disease, including active HCV infection, should not consume alcohol.

A positive response to either of the two questions above should prompt additional screening with other short screening tools (see the Screening and Assessment Tools Chart from the National Institute on Drug Abuse). These tools can identify substance use and guide decisions on appropriate treatment interventions. Currently, there are not enough data to determine how often people with HIV should be screened for SUDs; however, given the potential negative impact that SUDs may have on people with HIV, it is advisable to ask these questions during every clinical visit.

Health care providers should be nonjudgmental when discussing substance use with people who have HIV **(AIII).** People with HIV who experience stigma or judgment may lose trust in their health care provider's advice, avoid future visits, and consequently experience poorer health outcomes.[19] Language is one way in which stigma is communicated, and words such as "addict" and "dirty urine" convey a negative connotation. The Office of National Drug Control Policy (ONDCP), American Medical Association, American Society of Addiction Medicine, International Society of Addiction Journal Editors, and others have recommended the adoption of clinical, nonstigmatizing language for substance use, as described in the *Changing the Language of Addiction* report from ONDCP.

Co-occurring Mental Illness

Many people who use substances have co-occurring mental health disorders, including a history of trauma that may drive or exacerbate their substance use. Conversely, ongoing use of substances can place individuals at risk for trauma, such as sexual assault and sexual exploitation, which may further

exacerbate their substance use.[6,20] People with SUDs should undergo evaluation and treatment for concurrent mental health disorders using standardized screening instruments (e.g., the Patient Health Questionnaire-2, or PHQ-2, for depression). Where applicable, clinicians should use available behavioral and pharmacological interventions to address mental health concerns, because recommending that people stop their substance use without providing treatment for underlying mental health conditions has very limited efficacy.[21]

Selecting, Initiating, and Maintaining Antiretroviral Therapy

Ongoing substance use is **not** a contraindication for prescribing ART. ART is recommended for all people with HIV to improve their health and to prevent transmission of HIV to others **(AI),** including sexual partners and individuals who share drug paraphernalia. These clinical, community, and individual benefits should encourage health care providers to initiate ART in all people with HIV who use substances. Although effective ART prevents sexual transmission of HIV, its effectiveness in preventing transmission through shared needles and shared use of other drug paraphernalia remains unknown.

For people actively injecting drugs, engagement in a syringe service program (SSP) can facilitate access and adherence to ART. SSPs primarily provide clean drug preparation and injection supplies to reduce transmission of HIV, HCV, and other bloodborne, skin, and soft tissue pathogens. As a regular point of contact for people with complex health and social challenges, SSPs also provide opportunities to offer other integrated health-related and social support services,[22] including those for treating SUDs.[23] For people with HIV, SSPs can be adapted to provide or link to rapid initiation[24,25] and maintenance of effective ART.[25]

When selecting ART regimens for individuals who use substances, clinicians should consider potential barriers to adherence (see Adherence to the Continuum of Care), comorbidities that could impact care (e.g., advanced liver disease from alcohol or HCV), potential drug–drug interactions, and possible adverse events that are associated with the medications. Providers and people with HIV should discuss adherence during multiple, nonjudgmental evaluations. In general, the use of simplified ART regimens should be considered to aid adherence. Regimens for people with SUDs should be easy to take, such as once-daily formulations, ideally as a single-tablet regimen,[26] and should have a high barrier to resistance and a low risk of hepatotoxicity **(AIII).** Adherence counseling should highlight the benefits of ART use, irrespective of concurrent substance use. While a reduction in substance use may improve adherence to ART,[27,28] ongoing use is not a contraindication to ART.

Long-Acting Antiretroviral Therapy

The development of long-acting (LA) injectable ART provides additional options for treatment. The combination of injectable cabotegravir (CAB) and rilpivirine (RPV) is an optimization option for people with HIV who demonstrate retention in HIV care and who are virologically suppressed on oral therapy (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression). Current U.S. Food and Drug Administration (FDA) approval for LA CAB/RPV is limited to individuals with expected good adherence and an ability to achieve virologic suppression on oral therapy prior to starting LA ART. Limited data from a small, ongoing observational study found that LA CAB/RPV leads to high levels of viral suppression in people with HIV who have struggled with adherence to oral ART and those who are viremic at treatment initiation, including people who use stimulants.[29] Of note, the clinic in this study provided a significant amount of social support to ensure adherence

to the LA CAB/RPV regimen (see Virologic Failure for additional details). It is not known if similar responses can be seen in clinics without the resources to provide a similar level of adherence support. Missing LA CAB/RPV doses or a delay in receiving scheduled injections may result in emergence of HIV drug resistance.[29]

The following factors should be considered when contemplating the use of LA CAB/RPV in people with HIV and SUDs:

- As with all treatment conversations, providers should discuss adherence with their patients during multiple, nonjudgmental evaluations.
- Providers and people with HIV should consider the impact of using LA CAB/RPV in the context of current or past substance use behaviors. Although some people may welcome or even prefer LA CAB/RPV,[30] one qualitative study highlighted that using a needle for administering LA CAB/RPV could be a trigger for people with a history of injecting illicit substances.[31]
- Studies utilizing LA CAB/RPV have included individuals with good adherence before starting the LA ART, but this should not exclude people with SUDs who are struggling with adherence from being considered for LA CAB/RPV. Rather, the clinical team should consider what additional support may be needed to help people with SUDs be successful with LA CAB/RPV and whether using LA ART without established viral suppression is warranted based on preliminary data (see Virologic Failure and Adherence to the Continuum of Care for additional details). Case management, patient navigators, and/or peer navigators should be considered to help people with HIV return for follow-up injections.
- Given the often unpredictable lifestyles of people with SUDs, clinical care teams should be flexible in scheduling injections or accommodating walk-ins for injections. However, it should be stressed, however, that the doses should be given within the mandatory 7 days before or after the scheduled LA CAB/RPV injection date.
- As for all people with HIV, hepatitis B virus (HBV) status should be evaluated before the initiation of LA CAB/RPV (see HBV/HIV Coinfection and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression for additional details). If not already immune or infected, HBV vaccination should be initiated while considering LA CAB/RPV, including in those with isolated hepatitis B core antibody (HBcAb).
- LA CAB/RPV is not recommended for people with HBV/HIV coinfection unless HBV-active drugs (i.e., tenofovir, entecavir) are included in the regimen.
- As depressive disorders have been associated with LA CAB/RPV in all populations, people with SUD also should be screened for depressive disorders and treated for depression if indicated.[32] If depressive disorders worsen while on LA CAB/RPV, reevaluation should occur to determine whether continued therapy with this regimen is advisable.

Importantly, despite emerging observational data, multiple knowledge gaps exist regarding the use of LA ARVs among people with HIV and SUDs. The results from the ongoing Long-Acting Therapy to Improve Treatment Success in Daily LifE (LATITUDE) Study (NCT 03635788) will provide clinical trial results to help inform the use of LA CAB/RPV among people with HIV and SUDs who have struggled with ART adherence.[33] Additional research is also needed to determine optimal methods for supporting ART adherence (including to LA ARVs) among people with HIV and SUDs. These research studies will need to take into consideration the combination of various interventions

(e.g., peer support, case management, pharmacotherapy for SUDs, housing) and the appropriate individual interventions needed to support overall ART adherence.

Commonly Used Substances and Their Impact on HIV and Antiretroviral Therapy

Health care providers should have a basic understanding of evidence-based pharmacologic and behavioral (e.g., cognitive behavioral therapy, motivational interviewing, motivational enhancement therapy, contingency management) treatments for different substances, including alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. The sections below discuss the impact of these substances on people with HIV and how these substances affect ART use.

Alcohol

Epidemiology

Alcohol consumption is common among people with HIV. Recent estimates indicate that >50% of people with HIV in the United States consume any amount of alcohol (range, 54% to 67%).[34,35] Among a sample of people with HIV across seven university-based HIV clinics in the United States, 27% of people screened positive for unhealthy alcohol use as determined by the AUDIT-C.[35] Unhealthy alcohol use includes a spectrum of consumption, including at-risk or hazardous use, heavy episodic use (binge drinking), and alcohol use disorder (AUD).[36]

Risk-Taking Behaviors, the HIV Care Continuum, and Comorbidities

Unhealthy alcohol use has been linked to HIV acquisition because it can increase the frequency of behaviors that put a person at risk for sexual transmission of HIV.[37-39] In a meta-analysis of 27 studies, any alcohol use, unhealthy alcohol use, and alcohol use in sexual contexts all were associated with condomless sex among people with HIV.[38]

In addition, unhealthy alcohol use has been associated with interruptions in all steps of the HIV care continuum, including lower adherence to ART.[40,41] Studies have demonstrated both temporal and dose-related relationships between alcohol use and adherence, where ART is more likely to be missed on a given drinking day and the day after drinking, with a stronger association on heavy (binge) drinking days.[42-44] The negative impact of unhealthy alcohol use on ART adherence is likely multifactorial and driven by the effects of intoxication, ARV regimen complexity, and patient perceptions of adverse interactions between alcohol and ARV drugs.[45-47] Studies also have demonstrated an association between unhealthy alcohol use and the loss of durable viral suppression,[48-50] greater time spent with a viral load >1,500 copies/mL after ART initiation,[51] increased risk of viral rebound, lower retention in care,[52,53] and increased mortality.[54-56] Unhealthy alcohol use alone (hazardous or AUD) and in combination with other common comorbidities, including viral hepatitis coinfection, can hasten liver fibrosis progression in people with HIV.[57,58] Finally, in general medical populations, unhealthy alcohol use complicates the management of diabetes mellitus, hypertension, mental health disorders, other substance use, and other chronic diseases, and it increases the risk for pneumonia, osteoporosis, a number of cancers (e.g., liver, head and neck, and breast cancers), and tuberculosis.

Management of Unhealthy Alcohol Use

Ongoing alcohol use is not a contraindication for a person to receive ART. However, treatment for unhealthy alcohol use may improve HIV treatment outcomes. Behavioral treatments for unhealthy alcohol use among people with HIV demonstrate a small but significant reduction in alcohol use[59,60] (see additional resources for alcohol management from the National Institute on Alcohol Abuse and Alcoholism and the Substance Abuse and Mental Health Services Administration [SAMHSA]). Pharmacotherapy also can reduce alcohol use among people with HIV. The FDA has approved three pharmacotherapies for AUD: naltrexone, disulfiram, and acamprosate (see Table 15 below).

Clinical trials have demonstrated the efficacy of naltrexone in reducing the number of heavy drinking days among those with HIV and among the general population. Naltrexone appears to be safe to use in people with HIV,[61,62] and it is not associated with significant drug–drug interactions or irreversible hepatotoxicity. However, it is not recommended for individuals with decompensated liver disease and should be used with caution in individuals with elevated transaminase levels. Use of naltrexone in people with HIV and AUD can improve HIV treatment outcomes.[63] In a randomized placebo-controlled trial of 100 prisoners with HIV who met the criteria for AUD, individuals who were provided depot naltrexone upon release from prison were more likely to achieve viral suppression at 6 months than the placebo group (56.7% vs. 30.3%).[62]

Data on the use of disulfiram and acamprosate among people with HIV are lacking. Notably, integrating treatment for AUD with treatment for HIV has been shown to increase the number of people who receive alcohol treatment medication, counseling, and formal outpatient alcohol treatment services. Integrating these treatments also may improve the likelihood that a person with HIV will achieve viral suppression on ART. A randomized controlled trial of 128 individuals with HIV and AUD compared an integrated stepped-care model of alcohol treatment in Veterans Administration HIV clinics to treatment as usual. At the end of treatment (24 weeks), integrated stepped-care resulted in more participants receiving pharmacotherapy for AUD and participating in counseling. Although differences in alcohol use and viral suppression were not seen at 24 weeks, at 52 weeks, integrated stepped-care was associated significantly with an increased number of alcohol-abstinent days, a decrease in the number of drinks per drinking day, and a decreased number of heavy drinking episodes. In addition, the participants in the stepped-care group had increased odds of achieving viral suppression (odds ratio [OR] 5.58; 95% CI, 1.11–27.99).[64]

Liver cirrhosis—whether related to chronic heavy alcohol use, viral hepatitis, or metabolic dysfunction–associated steatotic liver disease—can result in altered metabolism of ARV drugs. For those who have hepatic impairment due to alcohol-related liver disease, ART dosing should follow the recommendations in Appendix B, Table 10, which are based on Child-Pugh classifications.

Benzodiazepines

Epidemiology

While the specific epidemiologic data on the prevalence of benzodiazepine use among people with HIV are limited, benzodiazepine misuse is a growing public health concern due to its impact on both morbidity and mortality.[65] Benzodiazepines cause anterograde amnesia, defined as difficulty recalling events after taking the medication. Individuals do not develop tolerance to this neurocognitive effect, and long-term use of benzodiazepines may result in impairment of neurocognitive functioning.[66]

Risk-Taking Behaviors and the HIV Care Continuum

People who inject drugs and who also use benzodiazepines engage in riskier behaviors than people who inject drugs but do not use benzodiazepines; these behaviors may include paying for sex, sharing injection equipment with more people, and performing more frequent injections.[67] A cohort of 2,802 people who injected drugs was followed from 1996 to 2013. During that time, benzodiazepines were the substances with the greatest association with mortality.[68] In a study of opioid and benzodiazepine use and all-cause mortality among 64,602 veterans (16,989 with HIV and 47,613 without) from the Veterans Aging Cohort Study (VACS) cohort (October 2008 to September 2009), long-term benzodiazepine receipt was associated with increased mortality regardless of long-term opioid receipt.[69] The long-term neurocognitive impact of benzodiazepines on ART adherence among people with HIV is unclear, but prescribing a memory-impairing medication to people with HIV who are prone to neurocognitive impairments from other causes may increase the risk of poor ART adherence.[70] Benzodiazepines also are used illicitly to counteract the negative side effects of stimulants, such as cocaine and methamphetamine.[71]

Management of Benzodiazepine Use

Repeated use of benzodiazepines can result in physiologic dependence and life-threatening withdrawal in some people. When feasible, individuals who chronically use benzodiazepines should be slowly tapered off the benzodiazepines under the supervision of an experienced clinician. Different benzodiazepines have different potencies (e.g., alprazolam is more potent than diazepam) and, therefore, require different tapers in terms of length and graduated decrease in dosage.

Benzodiazepine and Antiretroviral Drug Interactions

Several pharmacological interactions between benzodiazepines and ARV drugs have also been described. For example, some benzodiazepines are cytochrome P450 (CYP) 3A4 substrates; thus, when these benzodiazepines are used with a ritonavir (RTV)-boosted or cobicistat (COBI)-boosted ARV drug, their half-lives and concentrations can increase significantly, leading to enhanced and prolonged sedating effects. See Drug–Drug Interactions for available data on benzodiazepine-related interactions.[72]

Cannabis and Cannabinoids

Epidemiology

Both medical and recreational cannabis (marijuana) use are prevalent among people with HIV.[73] Cannabis belongs to a class of compounds that activate cannabinoid receptors. This class, known as cannabinoids, also includes synthetic compounds, such as K2. In recent years, cannabinoids have become more popular. In 2009, two cannabinoids were reported to the National Forensic Laboratory Information System. By 2015, 84 compounds had been reported.[74] These compounds most commonly cause tachycardia, agitation, and nausea, but they have a wide range of psychiatric effects, including psychosis and paranoia.[75]

Risk-Taking Behaviors and the HIV Care Continuum

Cannabis has not been shown to negatively impact adherence to ART or a person's ability to achieve viral suppression. In one study, among 874 people with HIV, daily cannabis use did not predict lower

odds of ART use or achieving an undetectable HIV RNA level, except when combined with binge drinking.[76] Data from the Multicenter AIDS Cohort Study have supported the idea that marijuana use does not predict problems with adherence to ART or achieving viral suppression.[77] In some cases, however, cannabinoids have been listed as the cause of death in overdoses. While data are lacking among adults with HIV, the nationally representative 2015 Youth Risk Behavior Survey (which includes data from 15,624 adolescent students in Grades 9 to 12) found that students who had ever used synthetic cannabinoids engaged in riskier activities, including sex, than students who only used marijuana.[78] While the available data suggest that the use of marijuana is not associated with decreased adherence to ART,[79] data are lacking on the impact of synthetic cannabinoids on ART adherence. Finally, with the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these products, which may increase the risk of opioid overdose.

Management of Cannabis and Cannabinoid Use

Because of the aforementioned concerns regarding cannabinoid use, particularly the variety of compounds and neuropsychiatric effects, people with HIV should be discouraged from using cannabinoids until more data are available. No pharmacological treatment exists for cannabinoid use disorder; however, behavioral health treatment may be effective for some people.[80-82]

Club Drugs

Epidemiology

Club drugs are recreational substances that have euphoric or hallucinogenic effects or that are used to enhance sexual experiences.[5] The use of multiple club drugs or other drugs simultaneously is common. Although these substances are used by many different people with HIV, the majority of data come from MSM with HIV. The use of club drugs in this population has been shown to negatively impact HIV treatment.[83] Club drugs include MDMA, GHB, ketamine, benzodiazepines (see the benzodiazepine section above), and other drugs that are used to enhance sexual experiences (e.g., mephedrone, inhaled nitrates [poppers], and phosphodiesterase-5 inhibitors [PDE5] for erectile dysfunction). Survey data from users of club drugs also have revealed that efavirenz is purchased by people without HIV for its intoxicating effects.[84]

Risk-Taking Behaviors and the HIV Care Continuum

Club drugs have disinhibitory effects. Using club drugs increases the likelihood that a person will engage in high-risk sexual practices, which can increase the risk of HIV transmission. In addition, these disinhibitory effects can lead to poor ART adherence.[72,83,85]

Management of Club Drug Use

Treatment strategies for club drug use have not been well studied in controlled trials.[86] No recommended pharmacotherapies exist at this time, and the most common strategy for treating people who use club drugs is to employ the behavioral interventions that are used for other drug use disorders.

Club Drug and Antiretroviral Drug Interactions

MDMA, GHB, ketamine, and methamphetamine all have the potential to interact with ARV drugs because they are metabolized, at least in part, by the CYP450 system.[72,85] Overdoses secondary to interactions between club drugs (i.e., MDMA or GHB) and protease inhibitor–based ART have been reported.[72,87] For instance, using PDE5 or ketamine concurrently with potent CYP3A4 inhibitors, such as RTV or COBI, can potentiate the effects of these substances.[83]

Cocaine

See the discussion in the section on stimulants below.

Opioids

Epidemiology

Opioids remain a significant concern for people with HIV, both for the acquisition of HIV and as major contributors to morbidity and mortality. Overdose involving opioids is the leading cause of accidental death in the United States.[88] The appropriate use of opioids while caring for people with HIV and chronic pain is an important component of combating the opioid epidemic, but this subject is beyond the scope of this section. Please refer to additional resources, such as those from the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America.[89] To combat the opioid overdose epidemic, health care providers should prescribe naloxone for opioid overdose prevention for all people who are using opioids beyond the short-term treatment of acute pain.[3]

Risk-Taking Behaviors and the HIV Care Continuum

Many people who use opioids start by using opioid tablets (e.g., oxycodone) that are ingested orally or crushed and sniffed. Once tolerance develops, some individuals move from sniffing the crushed tablets to injecting heroin purchased on the streets. This transition from sniffing to injecting dramatically increases the risk of HIV and HCV infection.

Low-cost heroin is often a mix of heroin and higher-potency synthetic opioids, such as fentanyl.[88] Methamphetamines and cocaine also have been combined with fentanyl but at a lower rate than heroin.[90,91] With the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these as well. In all instances where fentanyl or other high-potency opioids are added to other drugs, the risk of overdose increases.

Although treatment for an opioid use disorder (OUD) can improve HIV treatment outcomes, it is not a prerequisite for treating HIV, as some people with HIV are able to adhere successfully to ART despite ongoing opioid use. Although ART coverage among people with HIV who injected drugs increased from 58% to 71% between 2009 and 2015, additional work is needed to improve ART coverage in this population.[92] Data from the Johns Hopkins HIV Clinical Cohort (2001–2012) demonstrated that in the early years of the cohort, people who injected drugs were less likely to be retained in care; however, this gap in retention had closed by 2012, and people who injected drugs and noninjectors had similar probabilities of being on ART and having a suppressed viral load during the later years of the cohort.[93]

Management of Opioid Use

FDA has approved three medications for the treatment of OUD that can help decrease or eliminate opioid use, reduce the risks of morbidity and mortality that are associated with opioid use, and improve HIV treatment success. These medications—collectively termed medications for opioid use disorder (MOUD)—include buprenorphine, methadone, and naltrexone (see Table 15 below). Buprenorphine and methadone are opioid agonists (the use of these drugs is termed opioid agonist therapy), whereas naltrexone is an opioid antagonist or "blocker." Both buprenorphine and naltrexone can be prescribed in the setting of routine HIV clinical care.[94] Prescribing buprenorphine requires specific training but no longer requires an X waiver (see the SAMHSA website for more information). Methadone must be prescribed through a licensed opioid treatment program (OTP). An OTP directory also can be found on the SAMHSA website.[95]

Use of buprenorphine or methadone can lead to reductions in risky behaviors associated with HIV transmission, psychosocial and medical morbidity related to OUD, and criminal behaviors. People who are receiving treatment for opioid use are already engaging with the health care system; therefore, they are more likely to initiate treatment for HIV and to be adherent to their ARV regimens. Both buprenorphine and methadone are cost-effective interventions at the societal level.[96] Methadone has better retention in SUD treatment than either buprenorphine or naltrexone, and it should be considered for individuals who do not achieve successful outcomes with buprenorphine or naltrexone.[97] Buprenorphine has a lower risk of overdose than methadone. In addition, it can be prescribed in primary care offices. People who are taking buprenorphine have significantly better retention in treatment than those who are taking daily oral naltrexone.[98] Although several randomized, controlled clinical trials have demonstrated efficacy for naltrexone when treating OUD, subsequent study results have been disappointing; one meta-analysis revealed that oral naltrexone was equivalent to placebo.[99] To address the adherence challenges with naltrexone, a depot formulation was created for monthly administration. This preparation has the potential to improve adherence; however, studies that compare opioid agonists (i.e., buprenorphine and methadone) to depot naltrexone as treatments for OUD have not been conducted. In a randomized, placebo-controlled trial in people with both HIV and OUD, participants who received at least three doses of depot naltrexone before discharge from prison achieved longer periods of continuous abstinence after transitioning from prison to the community than those who received either placebo or two or less doses of depot naltrexone.[62] On the basis of these data, methadone or buprenorphine generally are used as first-line agents for the treatment of OUD. Depot naltrexone is used as an alternative treatment for people who have been released recently from correctional facilities when other options are not available.

Important pharmacokinetic interactions between these medications (particularly methadone) and certain ARV drugs are listed in Drug–Drug Interactions.

Although medications remain the backbone of treatment for OUD, there is growing recognition of the critical importance of the social drivers of health and how they impact the willingness of people to engage in treatment with the medications discussed above. A recent randomized study of 114 people with HIV compared the effectiveness of different medications for the treatment of OUD to achieve viral suppression, finding that stable housing, high school–level education or greater, and income stability were associated with a greater reduction in opioid use.[95]

Xylazine and Opioids

Xylazine—a non-opioid analgesic utilized in veterinary medicine that is a commonly used adulterant in opioids and other substances—has become an emerging drug threat associated with the opioid epidemic.[100] The CDC has documented a 276% increase in the monthly percentage of illicitly manufactured fentanyl (IMF)–involved deaths where xylazine was detected.[101] Between 2020 and 2021, the Drug Enforcement Agency reported that xylazine-associated deaths increased by over 100% in all regions of the United States and over 1,000% in the South.[102] This growing body of data led the ONDCP to formally designate fentanyl adulterated with xylazine as an emerging drug threat.[103]

Xylazine is a substrate of CYP3A4 and, as such, when used with an ARV regimen including a CYP3A4 inhibitor, such as RTV or COBI, may lead to elevated levels and prolonged half-lives of xylazine.[104] For people with HIV who continuously use opioids in areas with high rates of xylazine-adulterated IMF, providers should weigh the risks and benefits of using ARV drugs with CYP3A4 inhibitors, given potential interactions and the increase in xylazine-associated adverse effects.

Opioid adulterants, such as xylazine, increase the risk of overdose. Although naloxone only reverses opioid effects, that alone may be sufficient to reverse the overdose. This highlights the need for universal access to naloxone and the active prescribing of naloxone by health care providers. The CDC maintains information about xylazine and how to reduce its harm on its website.[105]

Stimulants

Epidemiology

Cocaine and methamphetamine are powerful stimulants that have been associated with multiple detrimental effects among people with HIV, including accelerated disease progression, poor ART adherence, and lack of viral suppression. Cocaine powder is snorted or injected, whereas the free-base form (crack) is smoked. Methamphetamines can be taken orally or rectally, injected, or smoked. Cocaine and methamphetamine are commonly used with other substances, including alcohol, and can be combined with fentanyl, which increases the risk of overdose.[90,91] Individuals who use stimulants experience a sense of euphoria and may have heightened sexual desire and arousal. This can lead to disinhibited sexual behaviors, increasing the risk of HIV transmission.

The prevalence of stimulant use among people with HIV has been estimated to be 5% to 15% across multiple studies.[106-108] Methamphetamine use is more common among MSM,[109] and increased rates of cocaine use have been observed among ethnic and racial minorities and persons with a history of incarceration.[110]

Risk-Taking Behaviors and the HIV Care Continuum

People with HIV who use stimulants may experience multiple negative health consequences, including rapid development of dependence and adverse effects on multiple organ systems, particularly the central nervous and cardiovascular systems. Stimulant use is associated with neurocognitive impairment,[111] delirium, seizures, hemorrhagic strokes, and mental health disturbances, including anxiety, psychosis, and paranoia.

Stimulant use may independently lead to HIV disease progression even among people who are taking ART and have achieved viral suppression. Research to identify the cellular mechanisms responsible

for this is ongoing, but increased viral replication, direct effects on the immune system that lead to declines in CD4 T lymphocyte cell count, enhanced immune activation, and disruption of the blood-brain barrier, facilitating HIV entry into the brain, have been implicated.[112-116] Stimulant use has been associated with poor HIV continuum of care outcomes, including suboptimal rates of ART adherence,[117] retention in care, and viral suppression.[118-120] Lack of viral suppression, combined with the increased likelihood of risky sexual behaviors that occur under the influence of stimulants, poses a threat to the HIV treatment-as-prevention paradigm.[121]

Management of Stimulant Use

Several pharmacologic and behavioral interventions for stimulant dependence have been investigated, and some trials have included people with HIV. The results of pharmacologic interventions generally have been disappointing. No FDA-approved pharmacotherapy for cocaine use disorder currently exists, despite research on multiple drug classes, including antidepressants, antipsychotics, anticonvulsants, and dopaminergic medications (e.g., disulfiram).[122,123] Among people with HIV who use crack and opioids, medication-assisted treatment for OUD may improve ART adherence and viral suppression.[124,125] Limited evidence indicates that some pharmacologic interventions (e.g., methylphenidate, modafinil, bupropion, naltrexone)[126] can reduce methamphetamine use or cravings. A double-blind, placebo-controlled trial of extended-release injectable naltrexone plus oral extended-release bupropion in adults with moderate or severe methamphetamine use disorder demonstrated a higher response of methamphetamine-free urine samples compared to placebo; however, the overall response rate was low.[127] A double-blind randomized clinical trial on people with methamphetamine use disorder evaluated daily mirtazapine versus placebo in cisgender men and transgender women who have sex with men. Over 36 weeks of follow-up, daily mirtazapine use led to reduced methamphetamine-positive urine drug tests and concurrent reductions in sexual risk behaviors.[128] No specific recommended pharmacotherapy exists to treat stimulant use disorder in people with HIV.

Several behavioral interventions have shown promise in randomized trials. People with HIV who received motivational interviewing sessions, cognitive behavioral therapy, or a combination of the two experienced decreased stimulant use, improved ART adherence, and were less likely to engage in sexual transmission risk behaviors.[129] Contingency management has been shown to be effective in decreasing stimulant use among people with HIV, but the sustained effects on the reduction of stimulant use and improvements in ART adherence are less clear.[107,130,131] The addition of a positive affect intervention to contingency management, compared with an attention control condition, decreased HIV viral load among sexual minority men with HIV.[132] Technology-based interventions, such as text messaging, may have a role in supporting ART adherence and decreasing methamphetamine use among people with HIV, but further research is needed.[133] People with HIV who use stimulants benefit most from multidimensional interventions that target substance use, ART adherence, and risky sexual behaviors.[129]

Despite the challenges discussed above, people with HIV who use stimulants can achieve viral suppression with ART[120] and should be prescribed ART even if stimulant use is ongoing.

Tobacco

Epidemiology

The prevalence of tobacco smoking among people with HIV in the United States is approximately twice that of the general population (33.6% vs. 16.8%).[134] Prevalence is even higher among specific subgroups, including those who use alcohol and/or other drugs, those who have concurrent mental health disorders, and those of a lower socioeconomic status. Although smoking rates are declining overall in the United States, people with HIV are less likely to quit smoking than people in the general population.[134]

Associated Risks of Tobacco Use and HIV Infection

With respect to substance use and HIV, tobacco smoking is the biggest threat to health-related gains achieved through ART. Among individuals with viral suppression on ART, more years of life may be lost from continued smoking than from HIV infection itself.[135,136] Tobacco smoking among people with HIV is associated with an increased risk of numerous health conditions, including lung cancer and other smoking-related cancers, cardiovascular disease, and pulmonary disease. In a sample of 17,995 people with HIV on ART in Europe and North America, individuals who smoked had nearly twice the mortality of those who did not (mortality rate ratio 1.94; 95% CI, 1.56–2.41) with significant mortality attributed to cardiovascular disease and non-AIDS-related malignancy.[135] Importantly, tobacco cessation reduces the incidence of cardiovascular disease and smoking-related cancers (although definitive data on lung cancer are not available) and improves quality of life.[137-139]

Managing Tobacco Use

To maximize the survival benefits of ART, clinicians should consider using evidence-based behavioral and pharmacological[140-142] cessation strategies when treating people with HIV who smoke tobacco (see the tools and recommendations provided by the CDC and the U.S. Preventive Services Task Force and recent review).[143] These include (but are not limited to) advising the individual to quit smoking, using the five A's, employing motivational interviewing, and referring them to a tobacco quitline. Pharmacotherapies for smoking cessation (nicotine replacement therapy, bupropion, and varenicline) have few clinically significant interactions with ARV drugs and can lead to enormous reductions in morbidity and mortality if the person is able to stop smoking. Nicotine replacement is efficacious[144]; however, bupropion doubles rates of smoking cessation compared with nicotine replacement therapy.[145] Varenicline is a partial nicotine receptor agonist. In comparative studies, varenicline was more effective than bupropion in smoking cessation.[145,146] Clinical trials among people with HIV have found varenicline to be both effective and safe.[140,142] In a randomized controlled trial among 179 individuals with HIV who were assigned to receive 12 weeks of behavioral counseling and either varenicline or placebo, varenicline use led to an increase in the percentage of participants who achieved a 7-day abstinence period at 12 weeks (28.1% vs. 12.1%, OR 4.5; 95% CI, 1.83–11.2) and produced higher continuous abstinence between Weeks 9 and 12 (23.6% vs. 10%, OR 4.65; 95% CI, 1.71–12.67) compared to placebo.[142] Although significant between-group differences were not observed after 24 weeks, these data support the use of varenicline among people with HIV. Varenicline should be used in combination with relapse prevention strategies and other measures for long-term tobacco cessation.

Table 15. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction With ARV Drugs	Comments
Alcohol Use Disorder			
Acamprosate	666 mg PO three times a day *or* 333 mg PO three times a day for people with CrCl 30–50 mL/min	No significant interaction with ARV drugs expected.	**Contraindicated** in people with CrCl <30 mL/min
Disulfiram	250 mg PO once daily	Use with caution when prescribing an ARV oral solution that contains ethanol and/or propylene glycol (e.g., FPV, LPV/r, RTV).	Counsel people regarding disulfiram reaction when taken with alcohol; symptoms for the reaction may include flushing, tachycardia, nausea, vomiting, or hypotension.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Has the greatest efficacy of all FDA-approved medications for AUD.
Opioid Use Disorder			
Buprenorphine	Individualize buprenorphine dosing based on the person's opioid use. The dose range is 4–24 mg sublingually. Dosing is once daily or twice daily.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug–Drug Interactions for further recommendations.	Buprenorphine has 90% first-pass hepatic metabolism. Verify that the person is using the appropriate technique for sublingual administration before adjusting the dose, because improper administration will result in poor absorption and low drug levels.
Methadone	Individualize the dose. People who receive higher doses (>100 mg) are more likely to remain in treatment.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug–Drug Interactions for further recommendations.	QTc prolongation is a concern at higher doses. Methadone can be prescribed for OUD only by a licensed OTP.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Longer time of continuous abstinence in those who received depot formulation naltrexone compared with placebo after transition from prison to community.
Nicotine Use Disorder			
Nicotine Replacement Therapy	The FDA has approved a wide variety of nicotine replacement products. All formulations are effective.	No significant interaction with ARV drugs expected.	Work with the person to identify the route of delivery that they will use and find most helpful.

Table 15. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction With ARV Drugs	Comments
Bupropion	Start at 150 mg PO daily for 3 days, then increase to either 150 mg twice daily or 300 mg once daily (use only formulations that are approved for once-daily dosing).	Concentration may be reduced when used with ARV drugs that are CYP2D6 inducers. See Drug–Drug Interactions for further recommendations.	For optimal results, tobacco quit date should occur 1 week after starting therapy.
Varenicline	Titrate the dose based on tolerability until the desired effect is achieved. The goal is to reach a dose of 1 mg PO twice daily. Requires dose adjustment in people with CrCl <30 mL/min.	No significant interaction with ARV drugs expected.	For optimal results, tobacco quit date should occur 1 week after starting therapy.

Key: ARV = antiretroviral; AUD = alcohol use disorder; CrCl = creatinine clearance; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; FPV = fosamprenavir; LPV/r = lopinavir/ritonavir; OTP = opioid treatment program; OUD = opioid use disorder; PO = orally; QTc = QT corrected for heart rate; RTV = ritonavir

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Transgender People With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all transgender people with HIV to improve their health and reduce the risk of HIV transmission to sexual partners **(AI).**
• HIV care services should be provided within a gender-affirmative care model to reduce potential barriers to ART adherence and to maximize the likelihood of achieving sustained viral suppression **(AII).**
• Prior to ART initiation, a pregnancy test should be performed for transgender individuals of childbearing potential **(AIII).**
• Some antiretroviral drugs may have pharmacokinetic interactions with gender-affirming hormone therapy. Clinical effects and hormone levels should be routinely monitored with appropriate titrations of estradiol, testosterone, or androgen blockers, as needed **(AIII).**
• Some gender-affirming hormone therapies are associated with hyperlipidemia, elevated cardiovascular risk, and osteopenia; therefore, clinicians should choose an ART regimen that will not increase the risk of these adverse effects **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Because transgender and nonbinary people bear a disproportionate burden of HIV, it is important for HIV care providers to be knowledgeable about the specific HIV care needs of these individuals.

Terminology

Transgender people are broadly defined as those whose gender identity differs from their assigned sex at birth.[1-3] The terminology used to describe transgender identities continues to evolve over time and across geographical and cultural contexts.[3,4] The terms cisgender, cis man, and cis woman are used to describe people who identify with their assigned sex at birth. The terms used to describe women who were assigned male at birth include transgender women, trans women, transfeminine individuals, and women of transgender experience. The terms for men who were assigned female at birth include transgender men, trans men, transmasculine individuals, and men of transgender experience. Some individuals identify outside the gender binary of man or woman, describing themselves as gender diverse, gender nonbinary, genderqueer, or gender nonconforming. Other individuals may not have a fixed sense of their gender and may move back and forth among different gender identities; these individuals are described as gender fluid. Gender fluidity refers to the nonfixed, adaptable nature of gender identity and expression that can occur and is commonly seen during adolescence.[5] Agender people do not identify with having any gender and can use other terms, such as null gender or neutrois.

Gender affirmation describes processes whereby a person receives social recognition, value, and support for their gender identity and expression.[6] Gender affirmation is often described across several dimensions, including social (e.g., social support and acceptance, use of pronouns, names, or clothing

that align with their gender identity), medical (e.g., use of hormones or surgery), legal (e.g., legal name change or changing gender markers on identity documents), and psychological (e.g., the degree of self-acceptance and comfort with their gender identity).[7] Medical gender affirmation has been shown to improve mental health outcomes and measures of well-being in transgender individuals.[8,9]

Epidemiology

National surveys indicate that 1.14% of the U.S. adult population, representing 3 million people, identify as transgender.[10] Data from the Pew Research Center suggests that gender diversity is more commonly reported among adolescents and young adults, with approximately 5% of young adults (aged 18 to 29) expressing a gender that is different from the sex on their original birth certificate, compared to 0.3% of older adults (aged 50 or older).[11] Meta-regression modeling suggests that the number of people who are willing to report that they are transgender and/or gender nonbinary is likely to increase in the future.[12]

The most recent estimate of global HIV prevalence among transgender people is 19.9% among transgender women and 2.6% among transgender men.[13] In the United States, the highest prevalence was found among Black and Latina transgender women[14], although data among transgender men are more limited.[15] Data on HIV prevalence among nonbinary individuals is scant. Of 164 nonbinary adults who completed nationally representative LGBTQ surveys between 2016 and 2018, 3% self-reported having HIV; however, results should be interpreted with caution due to the small sample size.[16] In 2022, HIV diagnoses among transgender people accounted for approximately 2% of all diagnoses. Of transgender and nonbinary people diagnosed in 2022, 31% were aged 13 to 24 years.[17] HIV diagnoses increased among transgender and nonbinary people while remaining stable among other gender groups, and transgender women were the only gender group to experience an increase (20%) in HIV-related deaths since 2018.[17]

The Centers for Disease Control and Prevention (CDC) surveillance reports indicate that 83% of transgender and nonbinary people with HIV diagnosed at year-end 2022 had received some aspect of HIV medical care, and 67% were virologically suppressed, which is well below the National HIV Strategy goal of 95% viral suppression for all people with HIV. Transgender women were the gender group with the lowest percentage of receipt of care and viral suppression.[18] In 2022, the Ryan White HIV/AIDS Program (RWHAP) provided services for 11,085 transgender people, representing 2.8% of RWHAP clients.[19] Of these transgender clients, 2.3% were transgender women, 0.3% transgender men, and 0.2% with another gender identity (e.g., nonbinary). Among RWHAP participants, retention in care (73.5%) and viral suppression (86.4%) for transgender adults and adolescents were lower than the national averages (77.5% and 89.6%, respectively). Overall, existing data are limited and likely underrepresent the proportion of transgender people due to a lack of systematic collection of gender identity and possible reluctance to disclose transgender identities because of social stigma.[20]

HIV Care Continuum

Some studies have reported that transgender women with HIV are less likely than cisgender men to receive antiretroviral therapy (ART), be adherent to ART, and achieve viral suppression.[21-27] However, data from a large multisite cohort study suggest that transgender women who are effectively engaged in care may have similar, if not better, HIV outcomes than cisgender people in HIV care.[28] Another retrospective study of Medicare beneficiaries with HIV found that transgender beneficiaries had greater care engagement than cisgender beneficiaries.[29] These results suggest that

once transgender people are linked to care, they are as likely to achieve positive HIV outcomes as cisgender people.

However, transgender people may experience numerous barriers to health care access and viral suppression.[30-32] The CDC Medical Monitoring Project found that transgender women diagnosed with HIV were more likely than cisgender men with HIV to have unmet subsistence needs (e.g., housing, transportation).[33] Unmet needs for services were negatively associated with higher levels of ART nonadherence (adjusted prevalence ratio [aPR]: 1.39; 95% confidence interval [CI], 1.13–1.70) and detectable viral loads (aPR: 1.47; 95% CI, 1.09–1.98). Among transgender and nonbinary participants in RWHAP, retention in care was lowest among those with temporary (68.3%) or unstable (67.5%) housing, and viral suppression was lowest among people with unstable housing (73.6%).[19] For a more detailed discussion on social determinants of health and adherence to HIV health care appointments and medications, clinicians should refer to Adherence to the Continuum of Care.

Barriers to HIV Care and Treatment

Transgender people may avoid the health care system due to stigma and past negative experiences (e.g., being called the wrong name or pronoun, being verbally harassed, being asked invasive questions about being transgender, or having to educate their providers about transgender people).[14,31,34-37] For many transgender people, gender-affirming therapy (e.g., feminizing hormones) is a greater priority than HIV treatment and care.[38,39]

Concerns about adverse interactions between antiretroviral (ARV) drugs and gender-affirming hormone therapy are common among transgender people.[38] One study found that 40% of transgender women with HIV did not take their ARV drugs as directed due to concerns about drug–drug interactions, yet less than half had discussed this concern with their providers.[40]

Facilitating HIV Care Engagement

Gender Affirmation

Individuals are more likely to engage in HIV care when gender affirmation needs are met.[6,35] A national study of transgender people with HIV found that participants who work with HIV care providers who affirm their gender (e.g., providers who use their chosen name and pronoun) were more likely to be virologically suppressed.[39] Adherence to hormone therapy correlates with adherence to ART.[41,42] However, making access to hormone therapy contingent upon ART adherence is associated with a lower likelihood of viral suppression.[39]

Integration of HIV Care With Gender Care

According to research on transgender youth[35] and adults,[38] integrating HIV care with gender care facilitates treatment and is associated with higher rates of viral suppression. In addition to minimizing the number of provider visits and potentially stressful clinical interactions, care integration makes it easier to discuss concerns about drug–drug interactions between HIV treatment and gender-affirming medications. In instances where integrated care is not feasible, the ART prescriber should refer the individual to an appropriate hormone therapy prescriber. Collaboration between these two care providers may enhance the quality of care.

Peer Navigation

Peer navigation has been found to improve the likelihood of sustained viral suppression among key populations, including among transgender women.[43] Research including youth and adults suggests that having visible transgender staff in the clinical environment also facilitates engagement in care.[35]

Gender-Affirming Clinical Settings

HIV care services should be provided within a gender-affirmative care model to reduce potential barriers to ART adherence and to maximize the likelihood of achieving sustained viral suppression **(AII).** Concrete steps that clinicians can take include ensuring that registration forms and electronic medical records are inclusive of transgender and gender nonbinary identities, preferably using a two-step method that records both gender and sex assigned at birth.[44,45] A self-reported, electronic approach may facilitate the disclosure of gender identity. Clinicians should also ask people with HIV about their gender identity, chosen names, and pronouns, using developmentally appropriate language. However, before including these items in the electronic health record, clinicians should discuss with people with HIV the possibility of inadvertent disclosure to others, such as parents or guardians.[46]

> *Example of an affirming way to ask about chosen names and pronouns:*
>
> *"My name is Dr. Smith. I use she/her pronouns. What name would you like me to use for you? What pronouns do you use?"*

Clinicians and staff should avail themselves of resource lists, brochures, and other materials that meet the specific needs of transgender people with HIV.

Integrating hormone therapy with HIV services is the recommended practice; this requires HIV providers to become knowledgeable about hormone therapy and other aspects of gender-affirming services. When integration of HIV and transgender services is not possible, the individuals should be referred to clinicians who are knowledgeable in the field of transgender medicine. Both the World Professional Association for Transgender Health (WPATH) and GLMA: Health Professionals Advancing LGBTQ+ Equality (previously known as the Gay & Lesbian Medical Association) have provider directories that list endocrinologists, primary care providers, and psychiatrists who have expertise working with transgender populations.

Pharmacological Considerations

Hormone Therapy

Hormone therapy is an important aspect of gender-affirming care for many transgender individuals. Hormones facilitate the acquisition of the secondary sex characteristics that are associated with the affirmed gender. Several guidelines for hormonal treatment of transgender people have been published, including guidelines from the Endocrine Society[47] and WPATH.[3] Clinical outcomes, potential adverse effects, treatment goals, and the person's current hormone levels should be taken into account when determining the appropriate doses of hormone and androgen blockers. A clinician should be aware of the typical doses and routes of administration for all the hormones and androgen blockers that the person is taking, whether these medications are prescribed or not. All additional interventions (such as gonadectomy) should be documented. These interventions could potentially

increase the risk of ART-related adverse effects on cardiovascular and bone health. Table 16a provides a list of gender-affirming hormone therapies (GAHT) that are commonly used in practice.

Feminizing regimens that are used by transgender women and others who were assigned male at birth usually include estrogens and androgen blockers. Feminizing regimens result in breast growth, redistribution of body fat, softening of the skin, and a decrease in muscle mass.[3] These regimens do not reduce facial (beard) hair or change the voice. In the United States, oral, parenteral, or transdermal preparations of 17-beta estradiol, or, less often, conjugated estrogens, are the mainstay of gender-affirming medical care for transgender women. Spironolactone, a mineralocorticoid receptor antagonist with anti-androgen properties, is normally used for androgen blockade; alternatives include gonadotropin-releasing hormone (GnRH) agonists (e.g., goserelin acetate and leuprolide acetate). Cyproterone acetate is a steroidal anti-androgen that is frequently used outside of the United States. 5-alpha reductase inhibitors that decrease the production of dihydrotestosterone (e.g., finasteride or dutasteride) may be used to reverse scalp hair loss. Some people may request progesterone to assist with breast growth; however, this has not been proven to be effective.[44] When using feminizing regimens, the goal is to suppress the testosterone level to <50 ng/dL and reach a serum estradiol level in the physiologic cisgender female range of 100 pg/mL to 200 pg/mL.[47]

Masculinizing regimens for transgender men and others who were assigned female at birth involve parenteral or transdermal testosterone preparations. These regimens are designed to stimulate the growth of facial and body hair, increase muscle mass, and deepen the voice; use of these regimens also results in clitoral enlargement, vaginal atrophy, and amenorrhea.[47] When using masculinizing therapy, the target testosterone levels are recommended to be 400 ng/dL to 700 ng/dL.[47]

Table 16a. Common Gender-Affirming Hormone Therapies

Feminizing Drugs		Physical Effects
Estrogens	Estradiol, PO 17 β-Estradiol, transdermal (patch) Estradiol valerate, IM Estradiol cypionate, IM	Redistribution of body fat Breast growth Decrease in muscle mass and strength Softening of skin Decrease in spontaneous erection
Androgen Blockers	**Mineralocorticoid Receptor Antagonist** • Spironolactone, PO **5α-Reductase Inhibitors** • Dutasteride, PO • Finasteride, PO • Cyproterone acetate, PO* **GnRH Agonists** • Leuprolide, IM • Triptorelin, IM or SQ • Goserelin, SQ	

Table 16a Common Gender-Affirming Hormone Therapies

Masculinizing Drugs		Physical Effects
Testosterones	Testosterone enanthate, IM or SQ Testosterone cypionate, IM or SQ Testosterone undecanoate, IM Testosterone gel, transdermal	Fat redistribution Facial/body hair growth Deepening of voice Increased muscle mass Amenorrhea Vaginal atrophy Clitoral enlargement

* Not available in the United States

Key: GnRH = gonadotropic hormone-releasing hormone; IM = intramuscular; PO = oral; SQ = subcutaneous

Hormones and Antiretroviral Therapy

Studies that have examined interactions between exogenous estrogens and ART have predominantly focused on combined oral contraceptive use in cisgender women.[48] The data from these studies have been used to make predictions about the direction and extent of drug–drug interactions (see Table 16b). However, there are known differences between the pharmacologic characteristics of ethinyl estradiol, which is used in contraceptives, and 17-beta estradiol, which is used for gender affirmation. These differences may influence the accuracy of the predictions about the interactions between feminizing hormonal regimens and ART.[49]

Table 16b. Potential Interactions Between Common Gender-Affirming Hormone Therapies and Antiretroviral Drugs*

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs That May Be Affected by ARV Drugs	Clinical Recommendations and Other Considerations for GAHT or ARV Drugs
ARV Drugs With the Least Potential to Impact GAHT Drugs	All NRTIs **Entry Inhibitors** • IBA, MVC, T-20 **INSTIs (Unboosted)** • BIC, CAB (IM or PO), DTG, RAL **NNRTIs** • DOR, RPV (IM or PO)	None	No dose adjustments necessary. Titrate dose based on desired clinical effects and hormone concentrations. **Note:** Avoid IM buttock injections into sites with gluteal implants and/or soft tissue fillers.

Table 16b. Potential Interactions Between Common Gender-Affirming Hormone Therapies and Antiretroviral Drugs*

ARV Drugs That May Increase Concentrations of Some GAHT Drugs	• EVG/c • PI/c, PI/r • LEN	Dutasteride Finasteride Testosterone	Monitor for associated adverse effects; decrease the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs That May Decrease Concentrations of Some GAHT Drugs	PI/r **NNRTIs** • EFV, ETR	Estradiol	Increase the dose of estradiol as needed to achieve the desired clinical effects and hormone concentrations.
	NNRTIs • EFV, ETR	Dutasteride Finasteride Testosterone	Increase the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs With an Unclear Effect on Some GAHT Drugs	EVG/c PI/c	Estradiol	There is the potential for increased or decreased estradiol concentrations. Adjust the dose of estradiol to achieve the desired clinical effects and hormone concentrations.

Note: See Tables 24a, 24b, 24c, 24d, 24e, 24f, and 24g for additional information regarding drug–drug interactions between ARV drugs and gender-affirming medications.

* Only ARV drugs commonly used in clinical practice in the United States are included in this table.

Key: ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GAHT = gender-affirming hormone therapy; IBA = ibalizumab; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PO = oral; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; T-20 = enfuvirtide

Other Hormonal Therapy Considerations

Bone Health

Bone metabolism is influenced by sex hormones. Current recommendations for osteoporosis screening are based on age and sex and have not been studied in transgender populations, which include people who have used hormone therapy and/or undergone removal of their gonads. Studies investigating bone mineral density (BMD) changes in transgender women have shown inconsistent results, with the use of estrogens being associated with both elevations and declines in BMD.[50-52] In one study, transgender women had high rates of osteopenia even before initiating hormones, possibly due to low levels of physical activity and low vitamin D levels.[50] Transgender men receiving testosterone appear to maintain adequate BMD.[53] The risk for osteoporosis increases after gonadectomy for both transgender men and transgender women, especially if hormone regimens are stopped. Consequently, clinicians should consider early BMD screening in this setting. The use of GnRH agonists to delay puberty is associated with a reduction in BMD. Although BMD has been shown to improve after these agents are stopped and/or gender-affirming hormones are initiated, peak bone mass attainment may be reduced.[54,55]

When using the FRAX® tool, which requires a sex designation, expert consensus is that assigned birth sex should be used, because transgender people who initiate hormones in early adulthood have generally already achieved peak bone mass.[47,56] Transgender people with HIV should be screened for

osteoporosis by age 50 using dual-energy X-ray absorptiometry, in accordance with current primary care recommendations.[57]

Since the use of tenofovir disoproxil fumarate (TDF) has been associated with reductions in BMD in people with HIV, TDF should be used with caution in transgender people with risk factors for osteoporosis, or in those with established osteoporosis.

Interpretation of Laboratory Values

Interpretation of laboratory results requires special attention when reference ranges vary by sex. The sex listed on laboratory requisition forms typically corresponds with the gender listed on the insurance forms and may not reflect the person's current anatomical or hormonal configuration. Reference ranges have not been established for transgender individuals who are receiving gender-affirming hormonal or surgical interventions. Interpretation of laboratory results is dependent on the person's physiology, dose and duration of hormone therapy, and the specific test being performed.[58]

Renal Concerns

Gender-affirming hormones can affect estimates of glomerular filtration rates (eGFR) that rely on serum creatinine due to changes in muscle mass. In a systematic review assessing the impact of gender-affirming hormones on kidney function, transgender men showed a mean increase in serum creatinine levels of 0.15 mg/dL (95% CI, 0.00 to 0.29) at 12 months after GAHT initiation, compared to a decrease of -0.05 mg/dL (95% CI, -0.16 to 0.05) among transgender women.[59] Creatinine-based eGFR calculations may therefore overestimate glomerular filtration rates (GFR) in transgender women and underestimate it in transgender men using GAHT. Obtaining a measured GFR or using cystatin C–based eGFR calculations may be considered for people with marginal renal function who are taking gender-affirming hormones.

Cardiovascular Disease Risk

Transgender individuals may have elevated cardiovascular disease (CVD) risk due to both traditional risk factors and cardiometabolic effects associated with hormone use.[60] Rates of tobacco use are higher among transgender people than in the general population,[61] and exogenous testosterone has been associated with increased levels of low-density lipoprotein (LDL) and decreased levels of high-density lipoprotein (HDL) among transgender men.[62] Transgender women have a higher risk of venous thromboembolism and ischemic stroke, primarily associated with the duration of estrogen use.[63] Transgender women on estrogens may show an increase in serum levels of triglycerides and HDL and a decrease in levels of LDL.[62] The implications of these differences are unclear. For example, one small study found transgender women with HIV have altered biomarkers associated with systemic inflammation and CVD when compared to matched cisgender men with HIV.[64] Yet, another small study of people with HIV found that subclinical CVD pathophysiology was not elevated in transgender women taking estrogen when compared with matched cisgender controls.[65]

Assessment of cardiometabolic risk among transgender people with HIV can be complicated by hormone-induced changes in lipid levels, as well as sex-specific variations in levels of homocysteine and high-sensitivity C-reactive protein.[66] American Heart Association (AHA) guidelines recommend using sex-specific calculators to determine cardiovascular risk and guide interventions;[67,68] however, AHA guidelines do not provide guidance for transgender people whose assigned sex at birth may differ from their hormonal and/or anatomical sex.[69] The WPATH Standards of Care, Version 8,

recommends clinicians use their professional judgment to tailor such calculators to the needs of transgender and gender-diverse people, taking into consideration the duration of hormone use, dosing, serum hormone levels, current age, and the age at which hormone therapy was initiated.[3]

Providers should take CVD risk into consideration when selecting both ART regimens and GAHT regimens. For transgender people with an elevated CVD risk or a history of CVD events, ARV drugs that are associated with CVD should be avoided whenever possible. See Table 20 for a list of ARV drugs that are associated with an increased risk of CVD. See Table 21 for alternative ARV agents to use in individuals with CVD. In transgender women who have an elevated risk for CVD or who have experienced a CVD event, transdermal estradiol may be the safest option for hormone therapy, because it carries a lower risk of thromboembolism than other routes of administration.[70] Of the 7,769 people with HIV in the recent Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), 127 (1.6%) were identified as transgender.[71,72] However, sub-analyses by gender identity have not been published. For guidance on the use of statins in people with HIV based on the REPRIEVE results, please see Recommendations for the Use of Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People With HIV.

Pregnancy Potential

Important information on contraception, drug–drug interactions between ARV drugs and hormone therapy drugs, and pregnancy is provided in Women With HIV and in the Drug–Drug Interactions tables of the guidelines. Much of this information also applies to transgender and nonbinary individuals. Below are specific ART considerations for transgender and nonbinary people of childbearing potential. Clinicians who care for pregnant people should also consult the current Perinatal Guidelines for a more in-depth discussion and guidance.

Some transgender individuals use exogenous hormones and/or undergo gonadectomy for gender affirmation. Understanding exactly what interventions someone has undergone and the timeline for these interventions will clarify the person's potential for pregnancy. Transgender individuals without a uterus (by birth or by hysterectomy) do not have pregnancy potential. Ovulation may continue in the presence of hormone therapy in transgender people with a uterus and ovaries, and these individuals may retain their fertility.[1] Gender-affirming surgeries do not impair fertility unless the uterus, ovaries, and vagina are removed.[73,74]

All transgender people who have a uterus and ovaries and engage in sexual activity that could result in pregnancy should receive a pregnancy test prior to initiating ART **(AIII).** All ART-naive persons who are pregnant should be started on ART for their health and to prevent perinatal transmission. Transgender people of childbearing potential should be counseled about ARV drug use during pregnancy, and clinicians should consult the Perinatal Guidelines when designing a regimen **(AIII).**

Testosterone Exposure in Transgender Persons With Ovaries

Testosterone alone is not a reliable form of contraception, and pregnancies have been reported in transgender men following prolonged testosterone treatment. Testosterone is a teratogen and it is contraindicated in pregnancy. Clinicians should assess the reproductive desires and fertility potential of their transgender clients and provide accurate information on contraceptive and reproductive options.[75]

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Transplantation in People With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Panel's Recommendations and Key Considerations
• People with HIV who are eligible for solid organ transplant (SOT) or hematopoietic cell transplant (HCT) should have equitable access to transplant **(AII).**
• People with HIV should be managed by a multidisciplinary team before, during, and after transplant **(AIII).**
• Transplant candidates with HIV should be up-to-date on their vaccination schedule **(AIII).**
Antiretroviral Drug Considerations Before Transplant
• In preparation for transplant, HIV providers should review the transplant candidate's antiretroviral (ARV) history, efficacy of the current ARV regimen, prior HIV drug resistance results, ARV adherence, and the potential for drug–drug interactions **(AIII).**
• All ARV regimen changes should be guided by ARV history, along with current and prior HIV drug resistance testing results **(AIII).**
• If switching to an alternative ARV regimen is necessary, changes should be completed several weeks before the transplant whenever possible to minimize drug–drug interactions in the post-transplant period and to assure tolerability and efficacy of the new regimen before transplant **(BIII).**
• Tenofovir alafenamide (TAF) is preferred over tenofovir disoproxil fumarate (TDF) in transplant candidates and recipients due to the lower risk of affecting renal function and bone mineral density **(AII).**
• To avoid significant drug–drug interactions between ARV drugs and anticipated immunosuppressive therapies, chemotherapies (for HCT), and prophylactic regimens for opportunistic infections, the following should be considered: ○ Unboosted second-generation oral integrase strand transfer inhibitor (INSTI)–based regimens (i.e., with bictegravir or dolutegravir) are preferred in most people with HIV needing transplant **(AII).** ○ In general, potent cytochrome P450 (CYP) 3A4 inhibitors—including pharmacokinetic boosters, such as ritonavir (RTV) or cobicistat (COBI), and protease inhibitor (PI)-containing regimens—should be avoided **(AII).** ○ In general, non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (NVP), efavirenz (EFV), and etravirine (ETR), which are CYP3A4 inducers, should be avoided **(AII).**
Maintenance of Viral Suppression
• HIV viral suppression should be maintained before and after transplant **(AIII).***
• HIV providers with appropriate expertise should design alternative ARV regimen(s) that are likely to achieve viral suppression if post-transplant regimen changes are necessary **(AIII).**
Immediately Post-Transplant
• Immediately post-transplant, renal or hepatic function may fluctuate; close monitoring of these organ functions is recommended to ensure appropriate dosing of ARV drugs and other concomitant medications to avoid potential drug toxicities **(AIII).**
• Interruption of antiretroviral therapy (ART) post-transplant should be avoided **(AIII).**
• If interruption is necessary, all components of an oral ART regimen should be stopped simultaneously to avoid exposure to an incomplete regimen. The period of interruption should be kept to a minimal duration **(AIII).**
• If a person cannot swallow pills, providers should consider using oral liquid formulation if available; alternatively, some pills can be crushed or dissolved for administration orally or via an enteral tube **(AIII).**

Post-Transplant
• Therapeutic drug monitoring for immunosuppressive drugs should be performed to guide dosing adjustments, especially before, during, and after the start or switch of ARV drugs that may interact with immunosuppressive drugs **(AII).** • The burden of medication increases significantly post-transplant. Providers should continue to evaluate for potential drug–drug interactions and overlapping toxicities with the addition of new medications **(AIII).**   ○ When feasible, providers should consider consolidating ART using fixed-dose combination tablets and/or single-tablet regimens to minimize pill burden and bolster adherence **(AIII).**
Hepatitis B Virus or Hepatitis C Virus Coinfection
• All donors and recipients should be screened for hepatitis B virus (HBV) and hepatitis C virus (HCV) with a serological and/or nucleic acid amplification test, according to transplant guidelines **(AIII).** • Transplant candidates and recipients who are nonimmune to HBV (as measured by HBV surface antibody [HBsAb]) should be vaccinated, ideally before transplant **(AIII).** • HBV serology should be monitored after transplant for loss of HBsAb in order to guide the need for revaccination per professional society and transplant center guidelines **(AIII).** • Transplant recipients with active HBV infection should be treated with ARV regimens with anti-HBV activity before transplant and indefinitely after transplant **(AIII).** Use of nucleos(t)ide reverse transcriptase inhibitors (NRTIs) with activities against both HIV and HBV is strongly recommended unless contraindicated or not tolerated **(AIII).** • For management of recipients with HIV without HBV who receive an organ from a donor with markers of HBV infection, see guidance in the HBV-Positive and HCV-Positive Donors section below and follow appropriate institutional protocols. • All transplant candidates and/or recipients with HCV infection should be treated with direct-acting antivirals against HCV **(AII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*
* In some cases, it may be necessary to interrupt ART due to intolerance of or inability to administer ARV drugs pre-transplant, such as in end-stage liver disease or when enteral access is limited. In these situations, the HIV provider should design a regimen that will result in viral suppression after transplant and resume therapy as soon as feasible.

General Principles When Managing People With HIV Before and After Transplant

Below are some key principles to follow when caring for people with HIV before and after transplant.

- Ensure that people with HIV have equitable access to transplant.
- Utilize a multidisciplinary approach.
- Maintain HIV viral suppression.
- Select or maintain an antiretroviral (ARV) regimen to minimize drug–drug interactions.
- Be aware of changes in renal or liver function.
- Perform therapeutic drug monitoring (TDM) of immunosuppressants for all transplant recipients.
- Consider pill burden.
- Consider and address hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection.

- Prevent infectious complications post-transplant with updated vaccination and antimicrobial prophylaxis.

Outcomes of Transplant in People With HIV and the Importance of Equitable Access to Transplant

Before the introduction of potent antiretroviral therapy (ART), people with HIV were systematically denied solid organ transplantation (SOT).[1] When performed, SOT was linked to unfavorable outcomes,[2] partly attributed to the use of older antiretroviral (ARV) regimens that included protease inhibitors (PI), which interact with immunosuppressive medications, such as calcineurin inhibitors or mTOR inhibitors.[3] SOT also had unfavorable outcomes in people with HIV and HCV coinfection before the era of direct-acting antivirals (DAAs) for HCV treatment.[4] The use of PIs also affects the choice of DAAs for HCV treatment. In the era of integrase strand transfer inhibitors (INSTIs) with fewer drug–drug interactions and the widespread availability of DAAs for HCV, recent cohorts have shown a reduction in the disparity of transplant outcomes between people with and without HIV.[5-7]

In people with end-stage renal disease (ESRD), those with HIV are less likely to be referred for kidney transplant than those without HIV. With the use of potent ART, kidney transplant in people with HIV is associated with a survival benefit over chronic hemodialysis, with high rates of recipient and graft survival at both 1 and 3 years post-transplant.[8] Lower but acceptable rates of recipient and graft survival have been reported with long-term (between 5 and 15 years) follow-up when comparing kidney and liver transplantation outcomes in people with HIV compared with recipients without HIV. This difference was primarily driven by lower rates of survival in people with HIV/HCV coinfection before the use of DAAs for HCV treatment.[6,9] In retrospective studies conducted in the post-DAA era, rates of recipient and graft survival in liver transplant recipients with HIV/HCV appear to be similar to people with HIV without HCV.[5,6] Acute rejection rates for kidney transplant recipients are higher in people with HIV than in recipients without HIV.[10]

Hematopoietic cell transplants (HCTs) in people with HIV are now the standard of care in people with hematologic malignancies for which HCT is indicated.[11] In most reported prospective and retrospective studies in the combination ART era, HIV status does not appear to impact the outcome of autologous or allogeneic HCT with respect to nonrelapse mortality. Allogeneic HCT is particularly intriguing due to its potential to significantly reduce HIV reservoirs or even achieve a cure, particularly when complete chimerism is achieved and the donor is CCR5delta32 homozygous. It is important to note that acute and even life-threatening viral rebound can occur if ART is discontinued after HCT. Planned ARV interruptions should only be attempted in the setting of a clinical trial.[11-16]

Given the improved outcomes and benefits to quality of life and other measures associated with transplantation, transplant eligibility should be equitable between people with and people without HIV **(AII).** Infectious complications and malignancy risk remain a concern post-transplant. For discussion of transplantation from donors with HIV to recipients with HIV, see Solid Organ Transplant Considerations From Donors With HIV below.

Multidisciplinary Approach

With the complexity of care required before, during, and after transplant in people with HIV, a multidisciplinary team approach is recommended, including transplant-specific specialists such as nephrologists, hepatologists, hematologists, infectious disease and HIV specialists, transplant

surgeons, pharmacists, nurses, and social workers **(AIII).** This approach is to ensure favorable outcomes and to effectively prevent and manage adverse events.

Antiretroviral Therapy Before, During, and After Transplant

This section of the guidelines will focus on special considerations for ART use before, during, and after SOT or HCT in people with HIV.

Maintain HIV Viral Suppression

Before and after a transplant, it is crucial to ensure that HIV suppression is maintained **(AIII).** This involves continuing ART as prescribed and closely monitoring viral load. Consistent adherence to ART is essential to prevent HIV viral rebound and maintain overall immune health. However, interruption of ART may be necessary in certain situations, such as intolerance of or inability to take oral ARV drugs pre-transplant, which may occur in some people with end-stage liver disease or when enteral access is limited post-transplant. In these situations, an ART regimen that will result in viral suppression after transplant should be resumed as soon as feasible**.**

Antiretroviral History and Review of Drug Resistance Testing Results

Before transplant and before starting, stopping, or changing any ARV drug, it is essential to review the person's ART history and any current and previous drug resistance testing results. This review guides the selection of an appropriate ARV regimen that will maintain or result in viral suppression.

If a person with wild-type HIV achieves and maintains viral suppression after starting ART, it is generally safe to assume that no drug resistance mutations have developed during that time. However, for people who have experienced virologic failure in the past, it is important to thoroughly review their resistance test results and their clinical and virologic responses to previous regimens when designing a new treatment plan.

Cumulative resistance test results encompass all previous and current test results, including genotypic, proviral DNA genotypic (if available), phenotypic, and tropism assays. Proviral DNA genotypic resistance testing can be considered in people with HIV who have suppressed viral loads and no prior drug resistance or unknown ART history information. In individuals with multiple treatment failures, proviral DNA genotypic testing may be useful but should be interpreted with caution. For additional information on proviral DNA assays, refer to the Drug Resistance Testing section.

Using the ART history and resistance results, one should be able to design at least one future suppressive regimen if changes are necessary.

Minimize Drug–Drug Interactions

Transplant recipients require multiple medications to prevent organ rejection, graft versus host disease (GVHD), and opportunistic infections, and to manage post-transplant complications. Polypharmacy can result in a complex array of drug–drug interactions. Consultation with a pharmacist with expertise in transplant, oncology, and/or HIV is recommended to aid with assessing and managing these challenging drug interactions.

Transplant-related drug interactions are commonly mediated by the cytochrome P450 (CYP) enzyme system. Below are some key principles for managing these drug–drug interactions.

- Use an ARV regimen with the lowest potential for drug interactions with medications used post-transplant, such as immunosuppressants, certain chemotherapeutic agents (for HCT recipients), azoles, corticosteroids, and acid-reducing drugs.
- Unboosted, oral, second-generation INSTI-based regimens (i.e., bictegravir or dolutegravir [DTG]) are preferred for most people with HIV needing transplantation **(AII).**
- In general, potent CYP3A4 inhibitors, including pharmacokinetic (PK) boosters such as ritonavir or cobicistat and PI-containing regimens, should be avoided **(AII).**
- In general, non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., efavirenz, etravirine, nevirapine), which are CYP3A inducers, should be avoided **(AII).** Among NNRTIs, doravirine (DOR) has fewer drug–drug interactions; however, experience with DOR in the transplant setting is limited.
- To minimize interactions in the post-transplant period and to assure tolerability and efficacy of the new regimen before transplant, whenever possible, any necessary ARV switches should be completed several weeks before the transplant **(BIII).**
- Therapeutic drug monitoring (TDM) of immunosuppressants is recommended for all transplant recipients; this is particularly important when drug–drug interactions with ARVs are expected **(AII).** Consultation with a pharmacist is recommended.

Drug Interactions Between Antiretroviral Drugs and Immunosuppressants

Immunosuppressants such as cyclosporine, sirolimus, and tacrolimus are mainstays of therapy post-transplant to prevent organ rejection or GVHD and are metabolized by CYP3A4.[17] These immunosuppressants have a narrow therapeutic window for efficacy and toxicity, and their drug concentrations may be impacted by ARV drugs that are CYP3A4 inhibitors or inducers because significant changes in their exposure may occur. There are limited data and experience evaluating interactions between newer ARV drugs and immunosuppressants, including a lack of published studies or case reports.[18-20] Immunosuppressant dose and target drug levels depend on the type of transplant, time since transplant, transplant center-specific protocols, transplant recipients' medical conditions, and other factors. Table 17a provides information regarding expected interactions based on available data and theoretical estimates. Safe and effective use of immunosuppressants should be guided by TDM.

Table 17a. Drug Interactions Between Antiretroviral Drugs and Immunosuppressants Used Post-Transplant

	Overview of Interaction Potential	Tacrolimus	Sirolimus	Cyclosporine
NRTI	↔ NRTI ↔ Immunosuppressant	Initiate standard doses. Monitor renal function if used with TDF.	Initiate standard doses. Monitor renal function if used with TDF.	Initiate standard doses. Monitor renal function if used with TDF.

Table 17a. Drug Interactions Between Antiretroviral Drugs and Immunosuppressants Used Post-Transplant

	Overview of Interaction Potential	Tacrolimus	Sirolimus	Cyclosporine
NNRTI	↔ NNRTI **With EFV, ETR, and NVP** • ↓ Immunosuppressant expected **With DOR (A Weak Inducer)** • ↓ Immunosuppressant possible **With RPV** • ↔ Immunosuppressant	Initiate standard doses and adjust based on TDM. **With EFV, ETR, and NVP** • May need higher doses **With RPV** • Monitor QTc with RPV.	Initiate standard doses and adjust based on TDM. **With EFV, ETR, and NVP** • May need higher doses **With RPV** • Monitor QTc with RPV.	Initiate standard doses and adjust based on TDM. **With EFV, ETR, and NVP** • May need higher doses. **With RPV** • Monitor QTc with RPV.
PI (With COBI or RTV as PK Booster)	↔ PI ↑ Immunosuppressant requiring dose reduction and/or extending dosing interval	↑ ↑ Tacrolimus Switch to a non-PI/c or PI/r-based regimen. If not possible, consider initiating tacrolimus 0.5 mg PO every 5–7 days. Adjust based on TDM.	↑ ↑ Sirolimus Switch to a non-PI/c or PI/r-based regimen. If not possible, consider initiating sirolimus 1–1.5 mg PO once weekly. Adjust based on TDM.	↑ CsA Consider initiating reduced dose of CsA at 5% to 20% of standard daily dose. Adjust based on TDM.
INSTI	↔ INSTI **For BIC, CAB, DTG, or RAL** • ↔ Immunosuppressant **With EVG/c** • ↑ Immunosuppressant with EVG/c	**For BIC, CAB, DTG, or RAL** • Initiate standard doses and adjust based on TDM. **With EVG/c** • ↑ ↑ Tacrolimus expected • Switch to a non–EVG/c-based regimen. If not possible, consider initiating tacrolimus 0.5 mg PO every 5–7 days. Adjust based on TDM.	**For BIC, CAB, DTG, or RAL** • Initiate standard doses and adjust based on TDM. **With EVG/c** • ↑ ↑ Sirolimus expected • Switch to a non–EVG/c-based regimen. If not possible, consider initiating sirolimus 1–1.5 mg PO once weekly. Adjust based on TDM.	**For BIC, CAB, DTG, or RAL** • Initiate standard doses and adjust based on TDM. **With EVG/c** • ↑ CsA expected • Consider initiating reduced CsA at 10% to 20% of total standard daily dose. Adjust based on TDM.
Capsid Inhibitors	↔ LEN expected ↑ Immunosuppressant expected	No data to guide dosing Adjust based on TDM.	No data to guide dosing Adjust based on TDM.	No data to guide dosing Adjust based on TDM.

Table 17a. Drug Interactions Between Antiretroviral Drugs and Immunosuppressants Used Post-Transplant

	Overview of Interaction Potential	Tacrolimus	Sirolimus	Cyclosporine
CCR5 Antagonist, Fusion, Attachment, and Post-Attachment Inhibitors	↔ ARV drugs expected ↔ Immunosuppressant expected	Initiate standard doses. Adjust based on TDM.	Initiate standard doses. Adjust based on TDM.	Initiate standard doses. Adjust based on TDM.

Key: ↔ = No clinically significant change; ↓ = decreased; ↑ = increased; ↑ ↑ = greatly increased; ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; CCR5 = chemokine co-receptor 5; COBI = cobicistat; CsA = cyclosporine; DOR = doravirine; DTG = dolutegravir; EFV= efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PO = orally; QTc = QT corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring

Drug Interactions Between Antiretroviral Drugs and Other Transplant-Related Medications

Transplant recipients often require other medications that may interact with ARV drugs via the CYP450 system or through decreased oral absorption due to altered gastric pH. These include azole antifungals, chemotherapy drugs, corticosteroids, and acid-reducing agents. A summary of these commonly encountered interactions can be found in Tables 24a to 24g. The table below is not comprehensive and is meant to highlight commonly used drug classes in transplant recipients with HIV.

Table 17b. Drug Interactions Between Antiretroviral Drugs and Medications Commonly Used in Transplant Recipients

Drug Class	Examples	Effects of Interactions
Azole Antifungals	Isavuconazole Itraconazole Posaconazole Voriconazole	**CYP Inhibition (e.g., With RTV or COBI as PK Booster, Azoles)[a]** • ↑ Azole concentration, ↑ toxicities • ↑ ARV concentration possible, ↑ toxicities **CYP or Glucuronidation Induction (e.g., EFV, NVP)** • ↓ Azole concentration, ↓ efficacy
Chemotherapy	Busulfan Cyclophosphamide Etoposide[b]	**CYP Inhibition or Induction (e.g., With RTV or COBI as PK Booster)** • ↑ or ↓ Chemotherapy concentration with RTV, ↑ toxicities, or ↓ efficacy • ↑ Chemotherapy concentration with COBI, ↑ toxicities **CYP Induction (e.g., EFV, ETR, NVP)** • ↓ Chemotherapy concentration, ↓ efficacy

Table 17b. Drug Interactions Between Antiretroviral Drugs and Medications Commonly Used in Transplant Recipients

Corticosteroids	Dexamethasone	**Dose-Dependent CYP3A4 Induction** • ↓ ARVs that are metabolized by CYP3A4
	High-dose Prolonged Use Prednisone/Prednisolone	**CYP3A4 Inhibition (e.g., With RTV or COBI as PK booster)** • ↑ Steroid concentration, ↑ toxicities
Acid-Reducing Medications	PPI, H2 Antagonists	**Increase in Gastric pH** • ↓ Absorption of certain ARVs, including ATV or RPV. See Table 24a and 24b for recommended timing of administration if concomitant therapy is needed.

Key: ARV = antiretroviral, ATV = atazanavir; COBI = cobicistat; CYP = cytochrome P450; CYP3A4 = cytochrome P3A4; EFV = efavirenz; ETR = etravirine; H2 = histamine 2; NVP = nevirapine; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir

[a] CYP inhibition by azoles can ↑ concentrations of immunosuppressants and certain cancer chemotherapy drugs.

[b] The listed are frequently used conditioning therapy pre-hematopoietic transplants that have potential interactions with ART. For other chemotherapeutic agents, consult a clinical pharmacist with expertise in transplant-related drug–drug interactions.

Considerations When Switching Antiretroviral Drugs Due to Drug–Drug Interactions

To minimize immediate interactions in the post-transplant period, whenever possible, any necessary ARV drug switches should be completed several weeks before the transplant **(BIII).** Waiting at least five half-lives would allow for adequate elimination of any interacting ARV drugs and/or PK booster prior to transplant. Switching ART by at least several weeks before transplant also allows clinicians to assess the tolerability and efficacy of the new regimen. Clinicians should be aware that discontinuation of certain ARV drugs may reverse previously stable drug interactions, therefore other comedications may need to be adjusted. For example, a person's immunosuppressant dose may need to be increased if the clinician is discontinuing a PI-based ARV regimen or the dose may need to be decreased if the clinician is discontinuing certain NNRTI-based regimens.

Changes in Renal or Hepatic Function

Following a kidney or liver transplant or after HCT, there may be abrupt changes in renal or hepatic function that may require dose adjustments of one or more drugs, including certain ARV drugs. All NRTIs except for abacavir (ABC) primarily undergo renal elimination and should be adjusted for dynamic changes in renal function. During the post-transplant period, it may be necessary to use individual components of ARV drugs instead of single-tablet regimens or fixed-dose combinations to allow for appropriate dose adjustments. Tenofovir alafenamide (TAF) is preferred over tenofovir disoproxil fumarate (TDF) because it has a lower risk of affecting renal function **(AII).** Because the rate of renal or hepatic function recovery can differ among recipients and immediate fluctuations may occur post-transplant, regular monitoring of organ function is important to ensure appropriate dosing of ARV drugs and minimize adverse effects or reduced efficacy (refer to Appendix B, Table 12 for ARV dosing in renal and hepatic insufficiency).

Alternative Methods for Antiretroviral Drug Delivery Post-Transplant

Interruption of ART post-transplant should be avoided **(AIII)**. If interruption is necessary, all components in an oral ART regimen should be stopped simultaneously to avoid exposure to an

incomplete regimen. The period of interruption should be kept to a minimal duration **(AIII).** If an ARV regimen includes both oral and long-acting injectable drugs (e.g., lenacapavir [LEN] or ibalizumab [IBA]) and interruption of the oral drugs is necessary, the oral ARV drugs should be resumed as soon as feasible to avoid monotherapy with the injectable agent.

If a transplant recipient cannot swallow pills immediately post-transplant, providers should consider using oral liquid formulation if available, or crushing and administering ARV drugs (if possible) to administer orally or via an enteral tube **(AIII).** Only a few ARV drugs are available in liquid formulations (Appendix B, Tables 1–12). Although PK data are limited, some ARVs can be temporarily crushed or dissolved and immediately administered orally or via an enteral tube until the recipients are able to swallow whole tablets (see more on Crushing and Liquid Antiretroviral Formulations). For people who require administration of crushed ARVs over an extended period of time, more frequent HIV viral load monitoring is recommended. If adequate oral absorption is a concern, TDM of certain ARV drugs may be considered.

Pill Burden and Post-Transplant Medication Management

Medications required for preventing graft rejection or opportunistic infections following SOT or HCT add significant pill burden and potential cost through medication copays. The complex medication schedule may also lead to medication errors and increased risk for suboptimal adherence. When renal and liver function are more stable, switching to single-tablet regimens or a fixed-dose combination ARV regimen (e.g., TAF or TDF with lamivudine [3TC] or emtricitabine [FTC]), dosed separately pre-transplant, can help reduce pill burden. Assisting transplant recipients with medication coordination, such as using a single pharmacy for dispensing all medications; attempting to synchronize refills to minimize trips to the pharmacy; and utilizing services such as adherence packaging, medication delivery, and refill reminders can also facilitate adherence. Medication and adherence counseling for transplant recipients and caregivers at each medical encounter is essential to ensure safe and effective therapy.

Impact of Medications on Adverse Effects and Comorbid Conditions

Close monitoring and prompt management of drug-associated adverse events is critical for all transplant recipients. Transplant medications, ARV drugs, and other medications may have some overlapping effects that can increase the risk or severity of toxicity. This overlap may have both short-term and long-term effects. Electrolyte disturbances may occur with sirolimus, tacrolimus, and cyclosporine. Of note, TDF may cause Fanconi syndrome, which could exacerbate the electrolyte disturbances. Similarly, nephrotoxicity associated with tacrolimus may also increase with concomitant TDF use.[21] All immunosuppressants are associated with side effects, such as nausea, vomiting, and diarrhea. These gastrointestinal side effects may be worsened when combined with ARV drugs, particularly PIs. While some of these adverse effects may be mitigated with symptomatic treatment, risk can be lowered pre-emptively by avoiding PIs and using TAF over TDF whenever possible.

In the long-term, people undergoing transplant are at high risk of developing new cardiovascular disease, diabetes, or osteoporosis.[22-24] If those conditions were present before transplant, they may worsen post-transplant. ARVs and/or transplant medications may play a role in the worsening of these conditions. Dyslipidemias associated with sirolimus or tacrolimus may be compounded by lipid disturbances associated with PIs or NNRTIs, such as efavirenz.[25,26] Cardiovascular events have been associated with ABC in some studies.[27] Fracture risk may be increased if corticosteroids are used in

combination with TDF.[28] Since TDF may negatively impact bone mineral density,[28] TAF is preferred over TDF **(AII).** Management of comorbid conditions in transplant recipients is highly individualized. Clinicians must consider the risks and benefits of adjusting stable ARV regimens versus using other medications to manage complications. If ARV regimens are adjusted post-transplant, selecting agents that have minimal impact on transplant-related comorbidities is helpful in optimizing therapy. (For more information, see Table 21. Antiretroviral Therapy-Associated Adverse Effects That Can Be Managed With Substitution of Alternative Antiretroviral Agents)

Considerations for Long-Acting Antiretroviral Drugs

Several important factors should be considered when making decisions to initiate or continue transplant candidates on long-acting (LA) injectable ARV drugs, including cabotegravir (CAB) and rilpivirine (RPV) (typically used together as a complete ART regimen), IBA, and LEN. Experience with these LA ARV drugs in transplant candidates is limited, and these agents have not been studied in the setting of severe hepatic disease, ESRD, or post-transplant. The impact of fluctuations in renal function, hepatic function, and fluid shifts that may occur around the time of transplant on the PK of these LA ARVs is largely unknown. Additionally, it should be noted that because LA ARVs may be difficult to obtain in the hospital, administration must be carefully timed to avoid any medication access issues and treatment interruptions.

The benefits of initiating LA CAB/RPV pre-transplant should be weighed against potential risks. People who are stable on LA CAB/RPV prior to transplant may be maintained on their regimen and monitored closely. For individuals with very low platelet counts or who require anticoagulation, intramuscular (IM) injections of LA CAB/RPV may need to be postponed. In these cases, initiation of a bridging regimen with oral CAB and oral RPV until IM injections can be resumed may need to be considered. If oral CAB is not available, DTG may be used in its place.

Although there are occasions when a transplant recipient may not be able to take oral medications immediately post-transplant, in general, this should be resolved within a few days. There are no data on temporarily switching to LA CAB/RPV as a bridging strategy in this instance and, therefore, this strategy is not advised.

IBA and LEN are two LA ARV drugs approved for use in people with multiple drug-resistant HIV. IBA is given as an intravenous infusion every 2 weeks, whereas LEN is given as a subcutaneous injection every 6 months. These drugs should not be started post-transplant just to reduce pill burden without other indications for their use. Transplant candidates on ARV regimens containing LEN or IBA likely have very limited alternative treatment options and should continue these LA ARV drugs as scheduled, in combination with any oral ARVs that are part of their complete regimen.

Because LA ARV drugs have very long half-lives, abruptly stopping any oral ARVs can lead to functional monotherapy with the LA ARV drugs, which may result in viral rebound and resistance. Therefore, the oral background regimen should be continued. People undergoing transplant who are maintained on these medications should be monitored closely for adverse events, drug interactions, and HIV viral load suppression. Drug interactions are an especially important consideration with LEN, which is a moderate CYP3A4 inhibitor (see Table 17a). There is a prolonged period of drug interaction risk due to the extended presence of LEN in the body. Clinicians may inadvertently miss these interactions if they are unaware that LEN is part of the ARV regimen, as clinic-administered

injectable LA ARV drugs are often listed separately from other ambulatory prescription medications in electronic health records.

Prevention of Infectious Complications Post-Transplant

Vaccination

Vaccination is a critical tool for preventing infections in all transplant recipients; however, the timing and some aspects of the approach to vaccination differ between SOT and allogeneic bone marrow transplant (BMT) candidates.

Timing of Vaccination

After registering as a transplant candidate and before SOT, there is typically a waiting period that provides an opportunity to assess vaccination status and update the vaccination record. It is important to consult the Centers for Disease Control and Prevention for up-to-date and specific vaccination recommendations, which include those for individuals with end-stage organ disease or immunocompromising conditions. Following an allogeneic BMT, vaccination plays a crucial role in restoring immune function and protecting against infectious diseases. Notably, the goal of vaccination in allogeneic BMT is to induce immune responses by the new engrafted donor immune system, not the pre-existing (recipient) one. However, vaccination strategies can vary based on the recipient's specific condition, transplant protocols, and recommendations from the transplant center. After allogeneic BMT, vaccination schedules are typically planned in phases, starting after the initial recovery period. Following that, vaccines are usually administered sequentially based on the transplant recipient's immune reconstitution status.

General principles for both SOT and allogenic BMT include the following:

- Vaccine recommendations for both SOT and BMT candidates and recipients should follow the same guidance as those recommended for those without HIV.
- In addition to reviewing standard pre- and post-transplant vaccine strategies described by the American Society of Transplantation Infectious Diseases Community of Practice, the need for additional vaccines based on HIV status (e.g., meningococcus) and/or exposure-related risk factors (e.g., mpox) should be assessed (see Immunization section of the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV*).
- For people without HBV infection, HBV vaccination is important to maximize options for ARV simplification strategies that may involve tenofovir-sparing regimens.
- Inactivated vaccines, which do not contain live pathogens, are generally considered safe after BMT. These include vaccines such as influenza, COVID-19, pneumococcal, HBV, tetanus, and diphtheria, as well as the new recombinant zoster vaccine.
- Live vaccines—including the varicella-zoster virus (VZV) and measles, mumps, and rubella (MMR) vaccines—should be avoided in SOT recipients while on immunosuppressants and may not be recommended immediately after BMT due to the recipient's weakened immune system. The decision to administer live vaccines is based on the individual's clinical condition and time since transplantation.

Pre-transplant Screening for Infection Risk and Antimicrobial Prophylaxis

Prior to transplant, transplant candidates should undergo a detailed assessment for infection risk, including history of prior infections, travel history, and environmental exposures. Due to the increased risk of reactivation of latent infections (e.g., tuberculosis, Strongyloides), transplant candidates with HIV who are at risk for these latent infections should undergo screening to guide pre-transplant treatment to prevent reactivation and disease post-transplant. Active opportunistic infections are a contraindication for transplantation. Additionally, both HIV and the immunosuppression associated with transplant are risk factors for anogenital or cervical human papillomavirus-related malignancies.[29] Prophylaxis against bacterial, fungal, and viral diseases is a standard of care at transplant centers and is tailored to factors such as serostatus (e.g., cytomegalovirus) or geographic risk (e.g., coccidioidomycosis). Clinicians should also be aware of the risk for donor-derived infections, especially in the early transplant period.

For more information regarding the prevention and treatment of opportunistic infections and donor-derived infections, refer to the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV* and center-specific protocols.

Recipient Considerations

HBV and HCV Coinfection

Due to overlapping risk factors, HBV and HCV coinfection is common in people with HIV. Both HBV and HCV are causes of cirrhosis that may lead to the need for liver transplant, and are also associated with extrahepatic manifestations such as diabetes mellitus, polyarteritis nodosa, membranoproliferative glomerulonephritis, and cryoglobulinemic vasculitis, which may contribute to ESRD.[30,31] Immunosuppression and chemotherapy (in cases of HCT) associated with transplant may result in loss of control of either HBV or HCV. Flares of active HBV or HCV following liver transplant begin with rises in HBV or HCV viral load, often followed by elevations in liver transaminases,[32,33] and can result in shortened graft survival. In those with only markers of prior HBV infection (core antibody [HBcAb] positive) and without evidence of active replication, HBV may reactivate from a latent state. Rarely, fibrosing cholestatic hepatitis results in rapidly progressive liver disease in transplant recipients.[34-38]

Assessment for HBV and HCV coinfection should occur at entry into HIV care and periodically for those at risk; status should be updated during the pre-transplant period. Transplant candidates or recipients who lack immunity to HBV (as indicated by negative HBV surface antibody [HBsAb]), including those with HBsAb loss, should receive vaccination regardless of HBcAb status and ideally before SOT.[39] Despite repeated attempts at vaccination, some people with end-stage organ disease or immunosuppression do not respond serologically and thus may be at risk for flares. Those undergoing allogeneic HCT generally undergo vaccination after the procedure.[40] For additional information regarding ARV drugs for people with HIV/HBV coinfection, refer to the Hepatitis B Virus/HIV Coinfection section.

Candidate/Recipient Considerations

Candidate/recipient is HBsAg positive. In people with active HBV (HBV surface antigen [HBsAg]–positive) coinfection, it is important to include either TAF or TDF as part of the ARV regimen, with the goal of suppressing both viruses. Both TAF and TDF are active against HBV, and

either can serve as the only active agent for HBV, although they are often used in combination with 3TC or FTC in people with both HIV and HBV. If TAF or TDF cannot be included, another potent anti-HBV drug—entecavir—should be initiated. Entecavir has weak anti-HIV activity and is not considered part of the ARV regimen but can induce nucleoside resistance mutation (M184V) and thus should never be used without a fully active ARV regimen.[41] Due to the low barrier to resistance and high likelihood for viral rebound, the use of 3TC or FTC as the only anti-HBV drug in individuals with HBV/HIV coinfection **is not recommended.**

Maintaining regimens with anti-HBV activity before transplant and indefinitely after transplant is recommended for transplant recipients with HIV and active HBV infection due to the risk of HBV reactivation and the potential for severe liver damage, including fulminant liver failure.

Candidate/recipient is HBcAb positive, HBsAg negative, and HBsAb negative or positive. The risk of HBV reactivation in the transplant recipient depends on the type of transplant, the depth of immunosuppression, and the presence of HBsAb. For liver transplant recipients who are HBcAb positive without evidence of active HBV (negative serum HBsAg and HBV DNA), reactivation risks are considered negligible due to removal of the potential liver reservoir. By contrast, in non-hepatic transplant recipients with markers of past infection, reactivation may occur in up to approximately 5%, usually during the first year, when immunosuppression is most intense and in the absence of protective levels of HBsAb.[42] This risk can be further abrogated if anti-HBV agents are already part of the ART regimen and by boosting HBsAb levels with vaccination. For non-hepatic transplant recipients not already on agents with anti-HBV activity, periodic prophylaxis or monitoring (regular measurements of transaminases and if newly elevated, rapid HBV DNA) strategies may be deployed to the highest-risk recipients per institutional protocol.[43,44]

Candidate/recipient is HCV RNA positive. All transplant candidates and/or recipients with HCV infection should be treated with DAAs against HCV **(AII),** preferably prior to transplant. Exceptions to this principle might include select candidates awaiting liver transplant, with a short waiting time for transplant (e.g., high Model for End-Stage Liver Disease, or MELD, score),[45] or select candidates for non-liver transplants who elect to defer treatment to remain eligible for donor organs from HCV viremic donors,[46-48] per discretion of the transplant providers. For those deferring treatment for HCV before transplant, treatment should be initiated early in the post-transplant period.[49-51] Additional considerations for the care of people with HIV and HCV, including fibrosis assessment, are found in the Hepatitis C Virus/HIV Coinfection section.

Donor-Related Considerations

HBV-Positive and HCV-Positive Donors

Organs from donors with serologic or virologic markers of HBV or HCV infection may be considered when recipients have given informed consent and providers have determined that benefits outweigh potential risks.[52,53] Antiviral treatment for recipients prior to transplantation can help prevent or manage post-transplant infection. Additionally, monitoring for donor-derived transmission and close follow-up of the recipient post-transplantation are necessary to detect and manage any potential infection.

Donor is HBcAb and/or HBsAg positive. To expand the size of the donor pool, use of HBcAb positive/HBsAg negative organs has become common practice.[54] More rarely, donors who are HBsAg positive are also utilized.[55] Without prophylaxis or recipient immunity (presence of surface

antibody), the risk of HBV transmission from such donors is present for non-hepatic organs and is extraordinarily high for liver transplants. Strategies to mitigate the risk of donor-derived HBV include pre-transplant vaccination, nucleos(t)ide therapy, and—particularly for liver transplant recipients who receive HBsAg-positive organs—hepatitis B immunoglobulin.[56] Anti-HBV agent prophylaxis may be deployed for moderate to high-risk recipients, with the highest risk (liver transplant recipients) receiving lifelong nucleos(t)ide analogues. Organ recipients with HIV may continue on regimens that already include tenofovir; those on tenofovir-sparing regimens pre-transplant may require the addition of anti-HBV agents such as tenofovir or entecavir. 3TC or FTC alone is not preferred for this indication.

Donor is HCV antibody or HCV RNA positive. The safety of using organs from HCV antibody-positive donors in both HCV viremic and aviremic recipients has been established, especially with early initiation of antivirals in the post-transplant setting.[45-48,51,57-62] Although untreated chronic HCV infection may have an accelerated course in people with HIV and SOT, early and effective treatment abrogates this risk substantially. Transplant candidates with HIV without current HCV infection should consider accepting HCV viremic organs if prompt DAA therapy is available at their center (see the Hepatitis C Virus section for more information).

Solid Organ Transplant Considerations From Donors With HIV

Kidney transplantation demonstrates survival benefit compared to dialysis for people with HIV and ESRD.[63] Previously, the use of organs from donors with HIV was banned. After a successful study of transplanting kidneys from donors with HIV into recipients with HIV in South Africa, the U.S. HIV Organ Policy Equity (HOPE) Act was approved in 2013, amending the law to allow transplantation of organs from donors with HIV into recipients with HIV (HIV D+/R+) under research protocols.[64]

For transplant candidates, eligibility criteria for HIV D+/R+ transplantation are the same as standard transplant criteria. For donors, federally mandated research criteria require that donors do not have active opportunistic infections.[65] Organs from donors with any CD4 lymphocyte cell count or viral load are allowed; however, transplant teams need to consider the likelihood of any ART resistance in the donors and justify whether an ART regimen in the recipient will be effective and tolerated.[65] To date, INSTI resistance has been rare in deceased donors with HIV.[66]

Early studies have shown excellent outcomes of HIV D+/R+ kidney and liver transplantation.[64,67] Based on this, the federal Advisory Committee on Blood and Tissue Safety and Availability has recommended to the U.S. Department of Health and Human Services that HIV D+/R+ kidney and liver transplantation be moved outside of research and into clinical care.[68] Due to the paucity of outcome data, HIV D+/R+ heart or lung transplantation remains under research protocols for now.[68] HIV D+/R+ kidney transplantation has been shown to decrease wait times for transplant.[69] SOT candidates with HIV may therefore consider being listed at a center currently offering organs from donors with HIV, if feasible.

As organ allocation in the United States occurs at a national level, all people with HIV may register as organ donors regardless of their distance from these centers, as their organs would only be directed to transplant candidates with HIV.[70] In addition, people with HIV may be living organ donors under HOPE Act research protocols.[68,71]

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Women With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all people with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners without HIV **(AI).**
• When prescribing antiretroviral (ARV) drugs for women with HIV, clinicians should consider that some ARV drugs have significant pharmacokinetic (PK) interactions with hormonal contraceptives **(AII)** and hormone replacement therapy **(BIII).** Consult Tables 24a, 24b, 24d, 24e, 24f, and 24g for detailed recommendations and a summary of available data when selecting ARV and hormone combination therapy **(AIII).**
• Clinicians should discuss with women the possibility of weight gain after initiating or changing ART. Some women in general, and Black women in particular, experience greater weight gain with ART over time than men. Concerns for weight gain should not be a reason for deferring ART.
• A pregnancy test should be performed for women of childbearing potential before initiation of ART **(AIII).**
• When selecting or evaluating an ARV regimen for women with HIV of childbearing potential, clinicians should consider the regimen's effectiveness, the woman's hepatitis B status, the teratogenic potential of the drugs in the ARV regimen, and the possible adverse outcomes for the mother and the fetus if the woman becomes pregnant while receiving the regimen **(AII).**
• During pregnancy, an additional goal of ART is to maintain a viral load below the limit of detection throughout pregnancy in order to reduce the risk of HIV transmission to the fetus and newborn **(AI).**
• When selecting an ARV regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and PK data on the use of each agent during pregnancy. The risks and benefits of ARV use during pregnancy should be discussed with all pregnant women **(AIII),** and clinicians should consult the Perinatal Guidelines when designing a regimen **(AIII).**
• Achieving and maintaining viral suppression with ART while breastfeeding does not completely eliminate HIV transmission risk but does reduce it to less than 1% **(AI).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

This section focuses on some unique clinical and therapeutic issues to consider and basic principles to follow when caring for cisgender women with HIV. Cisgender women are defined as individuals who were assigned female at birth and who identify themselves as women. In this section, cisgender women will be referred to as "women." Some topics discussed in this section—such as contraception, drug–drug interactions between antiretroviral (ARV) drugs and hormonal therapy, and pregnancy—also apply to transgender men (men assigned female at birth) and individuals assigned female at birth who identify as nonbinary (gender identities that are not exclusively feminine or masculine) or gender fluid (gender identity is not fixed). See Transgender People With HIV for more information on the specific HIV care needs of these individuals. Clinicians who care for pregnant people with HIV should consult the Perinatal Guidelines for a more in-depth discussion.

Sex Difference Considerations in Antiretroviral Therapy

In general, studies to date have not shown sex differences in virologic responses to antiretroviral therapy (ART).[1-6] However, limited data show that pharmacokinetics (PK) for some ARV drugs may differ between men and women, possibly because of variations in factors such as body weight,

plasma volume, gastric emptying time, plasma protein levels, cytochrome P450 activity, drug transporter function, and excretion activity.[6-10]

Adverse Effects

Several studies with older ARV drugs have suggested that sex may influence the frequency, presentation, and severity of some ARV-related adverse events.[11-13] In the ICONA cohort, people with HIV treated with dolutegravir (DTG)-based regimens were followed for up to 4 years. There was a higher risk of DTG discontinuation due to toxicity in both ART-naive and ART-experienced women compared with men.[14]

Some studies have investigated how metabolic complications that are associated with the use of ARV drugs differ between women and men. Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and some ARV drugs.[15-18] ARV regimens that contain tenofovir disoproxil fumarate (TDF), ritonavir-boosted protease inhibitors (PI/r), or both are associated with a significantly greater loss of bone mineral density (BMD) than regimens that contain other nucleoside reverse transcriptase inhibitors (NRTIs) and raltegravir (RAL).[19-22] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide (TAF) may be considered as alternatives to TDF for patients who are at risk of osteopenia or osteoporosis. Recommendations for the management of bone disease in people with HIV have been published.[23]

Weight Gain and Antiretroviral Therapy

Weight gain after initiation of ART, especially in people with advanced HIV, can be a sign of a return to better health. However, data from clinical trials and longitudinal cohort studies suggest sex differences in ARV-associated weight gain across all classes of ART among treatment-naive individuals, particularly with the use of certain integrase strand transfer inhibitor (INSTI)–based regimens (DTG and bictegravir [BIC]). In a pooled analysis of eight randomized controlled trials with ARV-naive people initiating HIV treatment, female sex was associated with 1.5 times the odds of a ≥10% weight gain compared with male sex (17.4% vs. 12.2%), with Black females significantly more likely to experience a ≥10% weight gain than non-Black females (19.7% vs. 12.4%).[24] At 144 weeks of follow-up in the ADVANCE study, a 12.3-kg weight gain was recorded among women receiving TAF/emtricitabine (FTC)/DTG compared with 7.4 kg and 5.5 kg among women receiving TDF/FTC/DTG and TDF/FTC/efavirenz (EFV), respectively.[25] In addition to women being more likely to experience weight gain with ARV initiation, the pattern of weight gain differs between men and women. In the ADVANCE study, at 96 weeks of follow-up, women gained more fat than lean body mass than men, with weight gain concentrated in the limbs and trunk. ARV-associated weight gain similarly has been observed among virologically suppressed women switching to an INSTI-based regimen.[26-28] In the Women's Interagency HIV Study, virologically suppressed women who switched to INSTI-based ART or had an INSTI added to their regimen (n = 234) gained an average of 4.2 kg in body weight at the 2-year follow-up compared with 0.2 kg in women remaining on non-INSTI ART (n = 884).[27] Mean change in percent body fat (1.7% vs. 0.3%) and body circumference measures were also greater in the INSTI group than in the non-INSTI group. Investigators did not detect a difference in weight gain by individual INSTI.

It should be noted that, although randomized controlled trials and observational studies suggest that individuals receiving INSTI-based regimens experience greater weight gain than those receiving comparator regimens, significant uncertainty continues as to whether INSTIs are causing weight gain

or whether the comparator drugs are suppressing weight gain. For example, an analysis in the ADVANCE trial demonstrated that the greater weight gain observed in DTG- versus EFV-treated participants was dependent primarily on CYP2B6 polymorphisms, which are associated with slow EFV metabolism (and presumably higher EFV levels). Among those with rapid EFV metabolism genotypes, no evidence was found for a weight difference between DTG- and EFV-treated participants.[29] The underlying mechanisms for weight gain in people receiving an INSTI-based regimen, and their impact on cardiovascular diseases, diabetes, pregnancy-related outcomes, and age-related comorbidities among women with HIV are currently unknown.

Switching from TDF to TAF, regardless of whether participants took INSTI, non-nucleoside reverse transcriptase inhibitor (NNRTI), or PI combinations, was found to be associated with weight gain, particularly in women and people of African descent.[30] The extent of TAF-associated weight gain may be affected by baseline body mass index (BMI). Among participants of the Women's Interagency HIV Study (WIHS) cohort, weight and BMI rose among women with baseline BMI below 30kg/m^3 when transitioning to INSTI, TAF, or INSTI and TAF together.[31]

All these data indicate that ARV-associated weight gain should be a factor to consider when initiating or changing ART, particularly in Black women. Because some ART regimens are more likely to cause weight gain in women, clinicians should weigh the benefits and risks of a particular regimen when initiating or changing ART. However, concerns about weight gain should not be a reason for deferring ART.

Adherence to Antiretroviral Therapy

Some observational studies have found that women are more likely than men to have suboptimal adherence to ART. Defining adherence as missing no dose of ART in the prior 3 days, the Centers for Disease Control and Prevention analyzed data from the nationally representative Medical Monitoring Project (n = 12,394) by race and gender.[32] Race comparisons by gender indicated that women had consistently lower ART adherence than men of the same race. Adherence rates were 94% for White men compared with 88% for White women, 93% for Latino men compared with 88% for Latina women, and 89% for Black men compared with 87% for Black women. A Canadian study followed 4,534 individuals (including 904 women) for a median of 65.9 months and found that a significantly lower proportion of women relative to men were optimally adherent (57.0% vs. 77.1%).[33] In the analysis adjusted for ethnicity and injection drug use, female sex remained associated independently with suboptimal adherence. Women with HIV face multifactorial barriers to adherence. Increasing access to social services—such as food, housing, and transportation—has been associated with improved ART adherence, as have social support and good patient–provider relationships.[34,35] Another analysis of 6,186 women from the Medical Monitoring Project found that women aged 50 and older were more likely to be adherent to ART than women younger than 50.[36] However, menopausal symptoms have been associated significantly with suboptimal ART adherence in cross-sectional[37] and longitudinal studies[38] of older women with HIV. It also was noted that 68.8% of older women with HIV experienced symptoms of menopause, but only 17% received treatment for these symptoms. It is plausible that treating menopausal symptoms may improve ART adherence among older women with HIV.[38,39]

Antiretroviral Therapy Considerations in Adults and Adolescents With HIV Who Are of Childbearing Potential

All adults and adolescents with HIV who are of childbearing potential should be offered comprehensive reproductive and sexual health counseling and care as part of routine primary medical care. Topics for discussion should include safe sex practices, reproductive desires and options for conception, the HIV status of sexual partner(s), the use of effective contraception to prevent unplanned pregnancy, and maintaining viral suppression to optimize health in preparation for pregnancy. Counseling also should include discussion of special considerations pertaining to ARV use when using hormonal contraceptives, when trying to conceive, and during pregnancy (see the Perinatal Guidelines). Clinicians should discuss intentions regarding pregnancy with all people of childbearing potential, and a pregnancy test should be performed before initiating ART **(AIII).**

Antiretroviral Regimen Considerations for Individuals Who Are Trying to Conceive

ART should be initiated and viral suppression achieved prior to pregnancy whenever possible. People should be given information about the benefits and risks of initiating specific ARV regimens when trying to conceive so they can make informed decisions about their care (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers).

Earlier data from the birth outcomes surveillance study in Botswana raised concern about an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[40,41] At the time of the study, folate fortification of grains in Botswana was uncommon. Folate prescribed before conception was low (0.1% to 0.2%) among the study participants.[42] Updated results from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception was not significantly different from those on non-DTG regimens at the time of conception.[43] Because folic acid is known to prevent NTDs in the general population, all pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI).** In a small cohort of 69 U.S. women who had periconceptional or early-pregnancy DTG exposure and access to folic acid fortification of food and/or received folate supplementation, there was no increased risk of NTDs in exposed infants.[44]

EFV is teratogenic in nonhuman primates.[45] However, in humans, no increase in teratogenicity has been reported with the use of EFV. Based on drug-specific risk assessments by the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to EFV have been monitored with no detected increase in the risk of overall birth defects, including in cardiovascular and genitourinary systems. Individuals who become pregnant while on EFV-containing regimens should continue their current regimens **(BIII).**

Before initiating ART in a person of childbearing potential, clinicians should review the What to Start: Initial Combination Regimens for People With HIV section and the Perinatal Guidelines for information to consider when choosing an ARV regimen. The key recommendations are listed below:

For individuals who are trying to conceive, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating one of the following regimens, which are designated as *Preferred* regimens during pregnancy in the Perinatal Guidelines: DTG or darunavir/ritonavir (DRV/r) plus a dual NRTI combination (ABC/lamivudine [3TC], TAF/FTC, TDF/FTC, or TDF/3TC). DTG-based

regimens are associated with rapid, durable viral load suppression, which is important for maternal health and the prevention of perinatal HIV transmission. BIC/TAF/FTC is an alternative INSTI-based regimen. The use of long-acting injectable cabotegravir (CAB) with rilpivirine (RPV) has not been studied in pregnancy.

For individuals who are not planning to conceive but who are at risk for pregnancy, consider a regimen's effectiveness and tolerability the available data on potential teratogenicity, and the person's preferences (e.g., pill burden) when choosing between regimens that are recommended for initial therapy (see Tables 6a and 6b in the Initial Combination Antiretroviral Regimens for People With HIV section). Clinicians should refer to the Perinatal Guidelines for recommendations.

Reproductive Options for Couples With Differing HIV Status

Couples with differing HIV status should be informed of options to prevent sexual transmission of HIV while attempting conception. If the partner with HIV is on ART and has achieved sustained viral suppression, sexual intercourse without a condom allows conception with effectively no risk of sexual HIV transmission to the partner without HIV (see Antiretroviral Therapy to Prevent Sexual Transmission of HIV).[46-48] People with HIV who intend to prevent transmission by using ART need to maintain high levels of ART adherence and should be informed that transmission is possible during periods of poor adherence, treatment interruption, and viremia. Both partners should be screened for sexually transmitted infections (STIs) and receive appropriate treatment if STIs are diagnosed.

Hormonal Contraception

Safe and effective reproductive health and family planning services to prevent unplanned pregnancies and perinatal transmission of HIV are essential components of care for individuals with HIV of childbearing potential. These individuals should receive ongoing counseling on reproductive issues. Individuals who do not desire pregnancy currently but are sexually active or considering initiating sexual activity should be offered effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Individuals with HIV can use all available contraceptive methods (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs),[49] after consideration of potential drug–drug interactions as discussed in the next section (also see the Perinatal Guidelines).

Drug–Drug Interactions Between Hormonal Contraceptives and ARV Drugs

Interactions between some ARV drugs and hormonal contraceptives may reduce contraceptive efficacy. However, most data are generated from healthy-volunteer, short-duration PK studies, and clinical data regarding interactions between ARV drugs and hormonal contraceptives in women with HIV are limited. The magnitude of change in drug concentrations that may reduce contraceptive efficacy or increase the risk of adverse effects is not known for all forms of contraceptives, making the clinical implications of some ARV-hormone drug interactions challenging to predict.

Concerns about PK interactions between hormonal contraceptives and ARV drugs should not prevent clinicians from prescribing hormonal contraceptives for individuals on ART. However, an alternative or additional effective contraceptive method is recommended if significant interactions may occur between hormonal contraceptives and ARV drugs (see Tables 24a, 24b, 24d, 24e, 24f, and 24g). A summary of ARVs with known interactions with hormonal contraceptives is described below:

Combination contraceptives containing ethinyl estradiol and progestins, including combined oral contraceptives (COCs), transdermal patches, and intravaginal rings:[50,51]

- EFV significantly decreases progestin concentrations from both COCs and intravaginal rings, which may increase the risk of contraceptive failure. EFV did not reduce oral ethinyl estradiol exposure in one small study, but it reduced exposure when combined with an intravaginal ring, which may increase the risk of intermenstrual bleeding (spotting), particularly with ultra-low and low-dose estrogen-containing contraceptives.
- Elvitegravir boosted with cobicistat (EVG/c), and cobicistat-boosted PIs or PI/r decrease ethinyl estradiol levels, which may increase the risk of spotting, particularly with ultra-low and low-dose estrogen-containing contraceptives. However, these ARV regimens also increase progestin exposure, which preserves contraceptive effectiveness.
- Cobicistat- and ritonavir-containing regimens should be avoided with drosperinone-containing products because of an increased risk of hyperkalemia.
- Fostemsavir (FTR) increases ethinyl estradiol exposure, which may increase risk of thromboembolic events. Product labeling recommends a maximum dose of ethinyl estradiol of 30 mcg per day when combined with FTR.[52]

Progestin-only pills:[50,51]

- EFV significantly decreases concentrations of oral progestin pills, including emergency contraception, which may increase the risk of contraceptive failure.
- Cobicistat- or ritonavir-boosted ARV regimens may increase progestin exposure. The combination may be used without dose adjustment; monitor for progestin-related adverse effects.

Injectable contraceptives (depot-medroxyprogesterone):

- One study of EFV-based ART plus depo-medroxyprogesterone acetate (DMPA) did not find a significant reduction in medroxyprogesterone acetate (MPA) exposure. No change in DMPA dose or frequency is necessary.[53]
- For women receiving both rifampin and EFV for the treatment of tuberculosis and HIV, some experts suggest administering DMPA every 8 to 10 weeks instead of every 12 weeks.[54]

Progestin-releasing contraceptive implants:[50,51]

- EFV significantly decreases progestin concentrations released from a contraceptive implant. Cohort studies have found that women receiving EFV-based ART and contraceptive implants have a higher rate of unintended pregnancies than women receiving other ART combinations.[55,56]
- Cobicistat- or ritonavir-boosted ARV regimens may increase progestin exposure, but the combination may be used without dose adjustment.

Pregnancy

All women with HIV should receive ART early in pregnancy, regardless of their viral load or CD4 T lymphocyte (CD4) cell count, for their own health and for the prevention of perinatal HIV transmission and transmission of HIV to sexual partners **(AI).** ARV drugs reduce the risk of perinatal

HIV transmission by decreasing maternal viral load in blood and genital secretions.[57-59] Clinicians who are caring for pregnant adults and adolescents with HIV should review the Perinatal Guidelines.

Antiretroviral Regimen Considerations

In general, the recommendations for the use of ART in pregnant women are the same as those for women who are not pregnant. As in nonpregnant individuals, genotypic drug-resistance testing is recommended for all people who are pregnant before initiating ARV drugs **(AIII)** and for those with detectable HIV viral load while on ART **(AI).** However, if not yet on ART, ART initiation should not be delayed pending genotypic drug-resistance test results. The ARV regimen can be modified, if necessary, once the resistance test results are available **(BIII).** Unique considerations that influence recommendations on the ARV drugs to use during pregnancy include the following:

- Potential ARV-associated adverse effects for pregnant women, fetuses, and infants
- Need for strict adherence to the prescribed ARV regimen to avoid viremia and drug resistance, optimize health outcomes, and minimize the risk of perinatal transmission
- Limited long-term outcome data for infants who were exposed to ARV drugs *in utero*, especially for newer ARV drugs

Clinicians should review the Perinatal Guidelines for ARV drug recommendations for individuals who recently have received an HIV diagnosis or those who become pregnant while on ART. Selection of ARV drugs for women who are pregnant should be individualized according to specific ARV history, the results of drug-resistance assays, and the presence of comorbidities, as well as the individual's preferences for balancing known and unknown risks and benefits of an ARV regimen.

Because of data suggesting decreased drug levels during pregnancy and associated loss of virologic suppression, cobicistat-containing regimens, including EVG/c, ATV/c, or DRV/c, are not recommended for initiation during pregnancy.[60] A pregnant woman who has a suppressed plasma viral load on one of these regimens could continue the regimen with frequent (e.g., monthly) viral load monitoring. Alternatively, another regimen that is predicted to maintain viral suppression can be used for the duration of the pregnancy.

The use of long-acting (LA) CAB with RPV has not been studied in pregnancy. In clinical trials, participants who became pregnant were switched from LA CAB and RPV to an alternative oral ARV regimen throughout the remainder of their pregnancies. Based on the pharmaceutical company's clinical trials and compassionate program through March 2021, 25 pregnancies were reported (20 LA CAB/RPV and 5 during oral lead-in phase); in 4 cases, conception occurred during the washout period after treatment discontinuation. There were 8 elective abortions, 6 miscarriages, and 1 ectopic pregnancy. Among the 10 livebirths (9 LA CAB/RPV and 1 oral), 1 infant had congenital ptosis.[61] Individuals who become pregnant while on ART will need close monitoring, and their pregnancy outcomes should be reported to the Antiretroviral Pregnancy Registry.

If maternal HIV viral load is ≥1,000 copies/mL (or unknown) near delivery, intravenous infusion of zidovudine during labor is recommended, regardless of the mother's antepartum regimen and resistance profile and the mode of infant delivery **(AI).** Administration of combination ART should continue during labor and before a cesarean delivery (oral medications can be administered with sips of water during this time).

Clinicians who are treating pregnant individuals with HIV are strongly encouraged to report cases of prenatal exposure to ARV drugs (either administered alone or in combination) to the Antiretroviral Pregnancy Registry.

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for nonpregnant adults and adolescents. Maternal ART should be continued after delivery. For more information regarding postpartum management of HIV, refer to the Perinatal Guidelines.

Some studies have demonstrated that adherence to ART may decline during the postpartum period.[62-64] Clinicians should address ART adherence at each postpartum clinic visit, including an evaluation of specific factors that facilitate adherence or present as a barrier to adherence. Clinicians may recommend an intervention to improve adherence (see Adherence to the Continuum of Care).

Clinicians should discuss future reproductive plans and timing, the risks and benefits of conceiving on specific ARV medications, and the use of appropriate contraceptive options to prevent unintended pregnancy. If an LA reversible contraceptive—such as an implant or IUD—is desired by the person, it should be inserted before hospital discharge or during the postpartum visit if possible.

Infant Feeding

Clinicians should refer to the Perinatal Guidelines for detailed recommendations regarding initiation or modification of infant feeding. People with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about their desire for infant feeding. Replacement feeding with properly prepared formula or pasteurized donor human milk eliminates the risk of postnatal HIV transmission to the infant.

Breastfeeding is **not recommended** for women who are not virally suppressed or for those who develop a detectable viral load while breastfeeding because of concern for increased risk of HIV transmission through breast milk.[65] If viremia occurs during breastfeeding, the woman should be advised to replace breastfeeding with another mode of feeding. Viral load testing should be repeated and plasma genotypic resistance testing should be performed if the level of viremia allows for a test to be done.

HIV and Menopause

The population of people with HIV is aging; thus, the number of women with HIV who are experiencing menopause is increasing. The median age of menopause in the general U.S. population is 52.5 years.[66] Evidence suggests that women with HIV are reaching menopause at earlier ages than those who do not have HIV.[67,68] The WIHS, which included 3,059 participants, demonstrated that approximately 1% (n = 35) experienced premature menopause before age 41, 3% (n = 101) between ages 41 and 45, and 21% (n = 442) between ages 46 and 50. These participants self-reported low ranges of hormone replacement therapy (14%, 16%, and 7%, respectively).[39] However, other confounding factors may affect age of menopause in women with HIV, such as sociodemographic factors, illicit drug use, hepatitis C coinfection, smoking, and possibly ART.

A Canadian study of 229 women with HIV reported that the average age of menopause was 48 years, which was 3 years younger than the general Canadian population. Lower level of education and

hepatitis C coinfection were associated independently with menopause at <45 years of age.[69] In another study of 667 women with HIV in Rio de Janeiro, Brazil, 24% reached menopause during the observational period and 27% had early menopause (<45 years of age). The median age of menopause was 48 years of age. Age at menarche <11 years, cigarette smoking, chronic hepatitis C, and CD4 count <50 cell/mm^3 were associated significantly with an earlier age of natural menopause.[70]

Menopause is a high-risk period for osteoporosis, which may be exacerbated by HIV and/or ART. A small, randomized international multicenter study demonstrated a trend of increased BMD at the lumbar spine after a switch from TDF to TAF in peri- and early postmenopausal women with HIV.[71]

Defining the relationship between HIV and menopausal symptoms, mental health, and depression is complicated because of overlapping symptoms from HIV itself, effects of ART, other comorbidities, and substance use. Some studies suggest that women with HIV experience a greater burden of menopausal symptoms, including vasomotor symptoms, sexual dysfunction, and mood changes.[67,68,72] Other studies did not find differences between women with HIV and those without HIV.[73,74] Menopausal symptoms also have been associated with reduced adherence to ART and poor cognitive performance.[37,38,75,76]

No studies have shown evidence of estrogen deficiency (i.e., menopause) affecting CD4 count, plasma HIV viral loads, or response to ART.[77,78] Two small studies showed no difference in plasma levels of tenofovir and RAL between pre- and postmenopausal women.[79,80]

The use of hormone replacement therapy (HRT) is low among women with HIV.[38] Data are limited on drug–drug interactions between ART and estradiol as part of HRT, and drug interaction data with ethinyl estradiol cannot be extrapolated to the estrogens used for HRT because of differences in metabolism. Drug interactions between HRT and ART are possible, particularly regimens containing cobicistat, ritonavir, PIs, or some NNRTIs. See the drug–drug interaction Tables 24a, 24b, 24c, 24d, 24e, 24f, and 24g for predicted interactions and clinical recommendations.

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Considerations for Antiretroviral Use in People With Coinfections

Hepatitis B Virus/HIV Coinfection

Updated: September 12, 2024
Reviewed: September 12, 2024

Panel's Recommendations
• Hepatitis A, B, and C virus serologies should be performed for all people with HIV **(AIII).** • Before initiating or switching antiretroviral therapy (ART), all people who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication **(AIII).** • Because tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and lamivudine (3TC) are active against both HIV and HBV, an antiretroviral (ARV) regimen for people with both HIV and HBV should include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive ARV regimen **(AI).** • In people with HBV/HIV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII),** because HBV resistance to these drugs can emerge. • If TAF or TDF cannot be safely used, or if there is a desire to use a tenofovir-sparing ART regimen, entecavir should be used as the alternative HBV therapy **(BI).** Entecavir has weak activity against HIV. Using entecavir for HBV treatment without ART may result in selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when given to people with HBV/HIV coinfection **(AII).** • Adefovir **(AI)** or pegylated interferon alfa **(AIII) are not recommended** for people with HBV/HIV coinfection. • In people with HBV/HIV coinfection, the discontinuation of agents with anti-HBV activity may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; people with HBV/HIV coinfection should be advised against stopping these medications and should be carefully monitored during interruptions of HBV-active treatment **(AII).** • When switching or modifying an ARV regimen in a person with HBV/HIV coinfection, including switching to long-acting injectables, ARV drugs that are active against HBV should be continued **(AII)** or specific anti-HBV drugs, such as entecavir, should be initiated **(AII).** • HBV reactivation has been reported in people with HIV and prior exposure to HBV (positive hepatitis B core antibody, negative HBsAg) when HBV-active agents are withdrawn as part of an ART regimen. Regardless of hepatitis B surface antibody level, people with HIV and prior HBV exposure are at low risk for reactivation and the associated hepatitis, which can result in serious hepatocellular injury. A monitoring strategy is considered a safe and effective way to assess HBV reactivation in low-risk people **(BIII).** • HBV reactivation has been observed in people with HBV/hepatitis C virus (HCV) coinfection while receiving interferon-free HCV treatment. For this reason, all people initiating HCV therapy should be tested for HBV. People with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes two agents with anti-HBV activity before initiating HCV therapy **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Approximately 5% to 15% of people with HIV in the United States also have chronic hepatitis B virus (HBV) infection, defined as positive HBV surface antigen (HBsAg).[1-3] The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in people with HBV/HIV coinfection than in people with chronic HBV mono-infection.[4] Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T lymphocyte cell responses following the initiation of antiretroviral therapy (ART).[5,6] Liver-associated complications may occur due to immune reconstitution after initiation,[7,8] or HBV reactivation after discontinuation of antiretroviral (ARV) drugs that are active against both HIV and HBV.[9-14]

Recommendations for People With HBV/HIV

- All people with HIV should be tested for viral hepatitis, including hepatitis A virus (HAV), HBV, and hepatitis C virus (HCV). People without immunity to HAV or HBV should receive a full vaccination series **(AIII).**
- A survey of people with HIV/HBV coinfection in the United States revealed that 4.0% had a positive hepatitis D virus (HDV) serologic test, of which 41.7% had detectable HDV RNA.[15] Because HBV/HDV coinfection has been associated with serious liver complications, many experts recommend that people with HIV and chronic HBV be tested for HDV infection.[16,17] The recommended initial serologic test is an HDV antibody test, which, if positive, should be followed by HDV RNA testing. People with HIV and HBV/HDV coinfection should be referred to an expert in the management of viral hepatitis.
- All people with chronic HBV should be evaluated to assess the severity of HBV infection (see Hepatitis B Virus in the Adult and Adolescent Opportunistic Infections Guidelines). In addition, people with chronic HBV should be advised to abstain from alcohol, be screened for alcohol use disorder,[18] and be counseled on prevention methods that protect against both HBV and HIV transmission.[19]
- Before ART is initiated, all persons who test positive for HBsAg should be tested for HBV DNA by using a quantitative assay to determine the level of HBV DNA **(AIII),** and the test should be repeated every 3 to 6 months to ensure effective HBV suppression. The goal of HBV therapy with nucleos(t)ide reverse transcriptase inhibitors (NRTIs) is to prevent liver disease complications by sustaining the suppression of HBV replication. A large cohort study found that persistent HBV viremia while taking ART and high HBV DNA levels were associated with a higher risk of hepatocellular carcinoma (HCC), even if HIV was suppressed; whereas sustained HBV DNA suppression for ≥1 year was associated with a 58% reduction in HCC risk.[20] The most common reason for persistent HBV viremia in people with HBV/HIV coinfection on tenofovir alafenamide (TAF)– or tenofovir disoproxil fumarate (TDF)–containing ART is suboptimal adherence; thus, the primary focus in this setting should be on improving adherence.[21]
- Because HBV reactivation has been observed in people with HBV infection during interferon-free HCV treatment,[22,23] people with HCV/HIV coinfection and chronic HBV infection should receive ART that includes two agents with anti-HBV activity (such as TAF or TDF plus emtricitabine [FTC] or lamivudine [3TC]) prior to initiating HCV therapy **(AIII).** The diagnosis of HBV reactivation should be considered in people with current HBV infection who experience elevated liver transaminases during or immediately after HCV therapy.

Antiretroviral Drugs With Dual Activities Against HBV and HIV

The NRTIs TAF, TDF, FTC, and 3TC are active against HBV. Entecavir is an HBV nucleoside analog that has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicity than TDF,[24,25] although weight gain has been observed more frequently with TAF than TDF.[26,27]

The efficacy of TAF versus TDF in hepatitis B e antigen (HBeAg)–negative patients with HBV mono-infection was evaluated through a randomized controlled trial, involving both treatment-naive and treatment-experienced participants. In this study, TAF was non-inferior to TDF, based on the percentage of participants with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = 0.47$).[28] In another study, TAF was also non-inferior to TDF in HBeAg-positive people with chronic HBV mono-infection, with a similar percentage of participants achieving HBV DNA levels <29 IU/mL at 48 weeks of therapy (64% for TAF vs. 67% for TDF; $P = 0.25$).[29] In both studies, people on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than participants receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to 48 weeks also favored TAF.[28,29]

In people with HBV/HIV coinfection, (TAF or TDF) plus (3TC or FTC) can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, TDF is fully active for the treatment of people with known or suspected 3TC-resistant HBV infection, whereas 3TC resistance compromises the activity of entecavir against HBV.

Recommended Therapy

The combination of (TAF or TDF) plus (3TC or FTC) should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection **(AI).**[30-32] The decision whether to use a TAF- or TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and the acceleration of bone loss. In a switch study in people with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ARV regimen to the fixed-dose combination elvitegravir/cobicistat (EVG/c)/TAF/FTC maintained or achieved HBV suppression with improved eGFR and bone turnover markers.[33] See Appendix B, Table 12 for guidance on renal dosing of NRTIs. Although data on switching from a TDF-based to a TAF-based ARV regimen are limited, the data from the EVG/c/TAF/FTC switch study suggest that people with HBV/HIV coinfection can switch to TAF/FTC-containing regimens with a potential reduction in renal and bone toxicity while maintaining HBV suppression.

Alternative Therapy

If TDF or TAF cannot be safely used or if there is a desire to use a TAF- or TDF-sparing ART regimen**,** entecavir can be used as an alternative HBV therapy in addition to a fully suppressive ARV regimen **(BI).** Entecavir has weak activity against HIV; its use for HBV treatment without ART may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC.[34,35] Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when given to people with HBV/HIV coinfection **(AII).** Because entecavir and 3TC share a partially overlapping pathway to HBV resistance, it is unknown whether the combination of entecavir plus 3TC or FTC will provide greater virologic or clinical benefit than entecavir alone. In people with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day.[36] However, entecavir resistance may emerge rapidly in people with 3TC-resistant HBV

infection. Therefore, entecavir should be used with caution in such people, with frequent monitoring (approximately every 3 months) of the HBV DNA level to detect viral breakthroughs.[35]

Important Considerations

- Discontinuation of HBV-active NRTI drugs may potentially cause serious hepatocellular injury resulting from the reactivation of HBV.[37]
- Entecavir has activity against HIV. However, when entecavir is used to treat HBV in people with HBV/HIV coinfection who are not on ART, the drug may select for the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in people with HBV/HIV coinfection, entecavir must be used in addition to a fully suppressive ARV regimen **(AII).**[38]
- When 3TC is the only active drug used to treat chronic HBV in people with HBV/HIV coinfection, 3TC-resistant HBV emerges in approximately 40% and 90% of people after 2 years and 4 years on 3TC, respectively. Given the similarities between FTC and 3TC, these drugs should only be used in combination with other anti-HBV drugs **(AII).**[39]
- In people with HBV/HIV coinfection, immune reconstitution following the initiation of treatment for HIV and HBV can be associated with elevated liver transaminase levels, possibly because HBV-induced liver injury is primarily an immune-mediated disease.[40]
- Some ARV agents (especially older drugs, such as nevirapine, tipranavir, and high-dose ritonavir) can increase liver transaminase levels. The incidence and magnitude of these increases were higher with HBV/HIV coinfection than with HIV mono-infection.[41-43] The etiology and consequences of these changes in transaminases are unclear because the changes may resolve with continued ART. Nevertheless, some experts suspend the suspected agent(s) when the serum alanine transferase (ALT) level increases to 5 to 10 times the upper limit of normal, or at a lower threshold if the person has symptoms of hepatitis and/or new elevations in bilirubin. However, increased transaminase levels in people with HBV/HIV coinfection may indicate HBeAg seroconversion due to immune reconstitution; thus, the cause of the elevations should be investigated before medications are discontinued. In people with increases in transaminase, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe, as well as HBV DNA levels, which should decrease in the setting of immune reconstitution. Other causes of ALT elevation—such as HCV or HDV infection, alcohol use, metabolic dysfunction-associated steatotic liver disease, and hepatotoxicity from non-ARV agents—should also be considered.

HBV Drugs Not Recommended

Adefovir in combination with 3TC or FTC with a fully suppressive ARV regimen was studied in people with HIV/HBV coinfection.[30,44,45] Adefovir was associated with high rates of HBV treatment failure and a high incidence of renal toxicity. Therefore, the Panel **does not recommend** adefovir for people with HBV/HIV coinfection **(AI).** Pegylated interferon alfa monotherapy is a potential therapy for the treatment of HBV mono-infection; however, data on its use in people with HBV/HIV coinfection are limited, and tolerance of the therapy in people with HIV is a significant limitation to its use. As a result, the Panel **does not recommend** pegylated interferon alfa for people with HBV/HIV coinfection **(AIII).** Pegylated interferon alfa can remain a treatment option in rare cases and with the consultation of an expert.

Changing Antiretroviral Therapy

- **When switching or modifying an ARV regimen in a person with HBV/HIV coinfection:** ARV drugs that are active against HBV (TDF or TAF in combination with 3TC or FTC) should be continued **(AII)** or a specific anti-HBV drug such as entecavir should be initiated **(AII).**
- **When ARV medications that are active against HBV in people with HBV/HIV coinfection must be discontinued:** Withdrawal of HBV-active treatment in a person with chronic HBV infection **is not recommended (AII).** If TAF or TDF cannot be continued due to concern for safety or if there is a desire to use a TAF- or TDF-sparing regimen and entecavir cannot be used or if there is concern for entecavir resistance, the person's clinical course should be monitored with monthly testing of liver transaminases. The risk of HBV flare in this setting is highest in people with positive HBeAg and those with active HBV. If no anti-HBV ARV drug can be used, entecavir should be added to a fully suppressive ARV regimen to prevent HBV flare **(AII)**, especially in people with marginal hepatic reserve, such as those with compensated or decompensated cirrhosis.[37]

Screening for HBV Before Initiating NRTI-Sparing or NRTI-Limited Antiretroviral Regimens

HBV status should be evaluated in all people with HIV who are not known to have chronic HBV before the initiation of an NRTI-sparing or NRTI-limited ARV regimen (such as long-acting cabotegravir plus rilpivirine [LA CAB/RPV], dolutegravir [DTG]/rilpivirine [RPV], or DTG/3TC). Considerations for screening include the following:

- People with HIV should be screened for HBV infection, and if not already immune or infected (including those with isolated hepatitis B core antibody [HBcAb]), vaccination should be initiated while considering these new ARV regimens (see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines).

- People with HBV/HIV coinfection were not included in clinical trials that evaluated NRTI-sparing or NRTI-limited regimens. If LA CAB/RPV, DTG/RPV, or DTG/3TC are used in people with HBV coinfection, TAF, TDF, or entecavir should also be prescribed **(AII).** In people with prior exposure to 3TC monotherapy, TAF or TDF is preferred due to the risk of HBV resistance to 3TC; thus, there is a lower barrier of resistance for entecavir.

- People with HIV and prior exposure to HBV infection (negative HBsAg, positive HBcAb, and either positive or negative hepatitis B surface antibody [HBsAb]) are likely at low risk (<1%) of HBV reactivation and even lower risk of HBV reactivation hepatitis,[14] although there are insufficient studies to confidently estimate the risk in this population. Of people with HIV and prior exposure to HBV infection, those with positive HBsAb are at the lowest risk for HBV reactivation, although HBV reactivation has been described when HBV-active therapy is withdrawn as part of an ART regimen.[14]

- For individuals with prior HBV exposure, it is reasonable and feasible to incorporate ALT monitoring into the frequent laboratory testing already recommended after switching from ART with HBV NRTI therapy (TDF, TAF, or entecavir) to LA CAB/RPV, DTG/RPV, or DTG/3TC. An increase in ALT would warrant HBV DNA testing to assess for HBV reactivation hepatitis and immediate initiation of HBV therapy once reactivation is confirmed. A monitoring strategy is

considered a safe and effective way to assess for HBV reactivation in low-risk people **(BIII).**[46,47] The timeline for reactivation is not clear in this population. Monitoring every 1 to 3 months for 6 months after switching from HBV-active ART is consistent with current recommendations for low-risk people without HIV.

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Hepatitis C Virus/HIV Coinfection

Updated: March 23, 2023
Reviewed: March 23, 2023

Panel's Recommendations
• All people with HIV should be screened for hepatitis C virus (HCV) infection **(AIII).** Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected **(AIII).** • Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most patients with HCV/HIV coinfection, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count **(AI).** • Initial antiretroviral (ARV) regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for people with HIV who do not have HCV infection. However, when treatment for both HIV and HCV is indicated, the ARV and HCV treatment regimens should be selected with special consideration for potential drug–drug interactions and overlapping toxicities **(AIII)** (see discussion in the text below and in Table 18). • All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes assessing their liver fibrosis stage to guide the duration of therapy and to predict subsequent risk of hepatocellular carcinoma and liver disease complications **(AIII).** • Patients with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and hepatitis B core (HBcAb; total or Immunoglobulin G). Persons who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination **(AIII).** • HBV reactivation has been observed in people with HBV infection during HCV treatment with direct-acting antivirals. Accordingly, before initiating HCV therapy, patients with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes two agents with anti-HBV activity **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

The treatment of hepatitis C virus (HCV) infection is rapidly evolving. Patients with HCV/HIV coinfection treated with all-oral, direct-acting antiviral (DAA) HCV regimens can achieve sustained virologic response (HCV cure) at rates comparable to those in patients with HCV mono-infection.[1-3] This section of the guidelines focuses on hepatic safety and drug–drug interaction issues related to HCV/HIV coinfection and the concomitant use of antiretroviral (ARV) agents and HCV drugs. For specific guidance on HCV treatment, clinicians should refer to the HCV Guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

Approximately one-third of patients with chronic HCV infection progress to cirrhosis at a median time of <20 years.[4,5] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[6-9] A meta-analysis found that patients with HCV/HIV coinfection had a threefold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV mono-infection.[8] The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in patients with HCV/HIV coinfection, several studies have demonstrated that the rate of disease progression continues to exceed that observed in patients

without HIV.[10,11] Whether HCV infection accelerates HIV progression, as measured by the occurrence of AIDS-related opportunistic infections or death,[12] is unclear. With older ARV drugs, people with HIV and HCV coinfection experienced higher rates of hepatotoxicity than those seen in people with HIV but not HCV.[13,14] These higher rates have not been observed with the newer ARV agents that are currently in use.

Assessment of HCV/HIV Coinfection

All people with HIV should be screened for HCV infection using sensitive immunoassays licensed for the detection of antibodies to HCV in blood.[15] Patients who are HCV-seronegative but at risk for HCV infection should undergo repeat testing annually or as clinically indicated. Patients who are HCV-seropositive should be tested for HCV RNA using a sensitive quantitative assay to confirm the presence of active infection. Patients who test HCV RNA positive should undergo HCV genotyping and liver disease staging as recommended by the HCV Guidance.

- Patients with HCV/HIV coinfection should be counseled to avoid consuming alcohol.
- Patients with HCV/HIV coinfection also should be counseled about appropriate precautions to prevent transmission of HIV and/or HCV to others.
- Patients with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and hepatitis B core (HBcAb; total or Immunoglobulin G).
    - Patients with evidence of active HBV infection (HBsAg positive) should be further evaluated and treated with ART that includes agents with anti-HIV and anti-HBV activities **(AIII).**
    - Those who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination.
- Patients with HCV/HIV coinfection who are susceptible to hepatitis A virus (HAV) should be vaccinated against HAV.
- All patients with HCV/HIV coinfection are candidates for curative HCV treatment.

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

Initiation of ART for patients with HCV/HIV coinfection should follow the recommendations for all persons with HIV infection, considering the need for concurrent HCV treatment with oral DAA regimens, the potential for drug–drug interactions, and the individual's HBV status.

Considerations When Starting Antiretroviral Therapy

The same regimens that are recommended for initial treatment of HIV in most ART-naive persons also are recommended for patients with HCV/HIV coinfection. Special considerations for ARV selection in patients with HCV/HIV coinfection include the following:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug–drug interactions with the HCV treatment regimen (see Table 18 below).
- In patients with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, before initiating HCV therapy, patients with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes agents with anti-HBV activity (such as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide plus emtricitabine or lamivudine) **(AIII).**
- Patients with cirrhosis should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and considered for liver transplantation. Furthermore, hepatically metabolized ARV and HCV DAA drugs may be contraindicated or require dose modification in patients with Child-Pugh class B and C disease (see Appendix B, Table 12).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in patients with HCV/HIV coinfection than in those with HIV mono-infection. Individuals with HCV/HIV coinfection who have advanced liver disease (e.g., cirrhosis, end-stage liver disease) are at greatest risk for DILI.[18] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[19] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 4 to 8 weeks after initiation of ART and at least every 6 to 12 months thereafter, and more often if clinically indicated. Mild to moderate fluctuations in ALT and/or AST levels (<5 times upper limit of normal [ULN]) are typical in individuals with chronic HCV infection. In the absence of signs or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART, but they do warrant monitoring to ensure a return to baseline. Patients with significant elevations in ALT or AST levels (>5 times ULN), concomitant increase in total bilirubin, or concomitant symptoms (weakness, nausea, vomiting) should be evaluated carefully for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, alcoholic hepatitis). If these signs and symptoms do not resolve, ART should be discontinued.

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found in the HCV Guidance. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug–drug interactions when used in combination. Before starting HCV therapy, the ART regimen may need to be modified to reduce the drug–drug interaction potential. Table 18 below provides recommendations on the concomitant use of selected drugs for the treatment of HCV and HIV infection. In patients receiving ART that has been modified to accommodate HCV treatment, HIV RNA should be measured within 2 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After ART modification, initiation of an HCV DAA regimen should be delayed for ≥2 weeks. Resumption of the original ARV regimen also should be delayed until ≥2 weeks after the HCV DAA regimen is completed. The prolonged half-life of some HIV and HCV drugs poses a potential risk of drug–drug interactions if a regimen is resumed soon after ART modification or HCV treatment completion.

Table 18. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults With HIV

The recommendations in this table for concomitant use of select HIV drugs with U.S. Food and Drug Administration (FDA)–approved HCV DAA drugs are based on available pharmacokinetic (PK) interaction data or are predictions based on the known metabolic pathways of the agents. (Instances where PK interaction data are limited or not available are indicated in the table.) Whenever HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. Because the field of HCV therapy is rapidly evolving, readers also should refer to the latest drug product labels and the HCV Guidance for updated information.

Note: Interactions with fosamprenavir (FPV) and nelfinavir (NFV) are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV protease inhibitors (PIs).

ARV Drugs	Individual Drug	Coformulated				
				SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)		
	Sofosbuvir	**Ledipasvir/ Sofosbuvir**	**Sofosbuvir/ Velpatasvir**	**Sofosbuvir/ Velpatasvir/ Voxilaprevir**	**Glecaprevir/ Pibrentasvir**	**Elbasvir/ Grazoprevir**
3TC	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
TDF	✓	✓ Monitor for TDF-associated adverse events.	✓ Monitor for TDF-associated adverse events.	✓ Monitor for TDF-associated adverse events.	✓	✓
Unboosted ATV	✓	✓	✓	✖	✖	✖
ATV/r or ATV/c	✓	✓	✓	✖	✖	✖

Table 18. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults With HIV

ARV Drugs	Individual Drug	Coformulated				
				SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)		
	Sofosbuvir	**Ledipasvir/ Sofosbuvir**	**Sofosbuvir/ Velpatasvir**	**Sofosbuvir/ Velpatasvir/ Voxilaprevir**	**Glecaprevir/ Pibrentasvir**	**Elbasvir/ Grazoprevir**
DRV/r or DRV/c	✓	If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated adverse events.[a]	If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated adverse events.[a]	✓ If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor for TDF-associated adverse events.[a] Consider monitoring for hepatotoxicity.[b]	✖	✖
LPV/r	✓			✖	✖	✖
TPV/r	✖	✖	✖	✖	✖	✖
DOR	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓
EFV	✓		✖	✖	✖	✖
ETR	✓		✖	✖	✖	✖
NVP	✓		✖	✖	✖	✖
RPV PO and IM	✓		✓	✓	✓	✓
BIC/TAF/FTC	✓	✓	✓	✓	✓	✓
CAB PO and IM	✓	✓	✓	✓	✓	✓

Table 18. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults With HIV

ARV Drugs	Individual Drug	Coformulated				
				SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)		
	Sofosbuvir	**Ledipasvir/ Sofosbuvir**	**Sofosbuvir/ Velpatasvir**	**Sofosbuvir/ Velpatasvir/ Voxilaprevir**	**Glecaprevir/ Pibrentasvir**	**Elbasvir/ Grazoprevir**
DTG	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓
EVG/c/TDF/FTC	✓	✖	✓ If used with TDF, monitor for TDF-associated adverse events.	✓ If used with TDF, monitor for TDF-associated adverse events. Consider monitoring for hepatotoxicity.[b]	✓ If used with TDF, monitor for TDF-associated adverse events. Consider monitoring for hepatotoxicity.[c]	✖
EVG/c/TAF/FTC	✓	✓	✓	✓ Consider monitoring for hepatotoxicity.[e]	✓ Consider monitoring for hepatotoxicity.[f]	✖
RAL	✓	✓	✓	✓	✓	✓
MVC	✓	✓	✓	✓	✓	✓
FTR	✓	✓	✓	✖ Use alternative HCV regimen if possible.	✓	✖ Use alternative HCV regimen if possible.
LEN	✓	✓	✓	✓	✓	✓

[a] Consider using an alternative HCV treatment or ARV regimen to avoid increases in TDF exposure. If coadministration is necessary, monitor patient for TDF-associated adverse events.

[b] Voxilaprevir exposures can increase when it is coadministered with pharmacologically boosted DRV or EVG. Until more safety data in clinical settings become available, patients who are receiving voxilaprevir and pharmacologically boosted DRV or EVG should be monitored for hepatotoxicity.

Table 18. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults With HIV

[c] Glecaprevir exposures can increase when it is coadministered with EVG/c. Until more safety data in clinical settings become available, patients who are receiving glecaprevir and EVG/c should be monitored for hepatotoxicity.

Key to Symbols:

✓ = ARV agents that can be used concomitantly
✖ = ARV agents not recommended
? = Data on PK interactions with ARV drug are limited or not available
↑ = Increase
↓ = Decrease

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; DAA = direct-acting antiviral; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; FTR = fostemsavir; HCV = hepatitis C virus; IM = intramuscular; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PO = oral; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

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Tuberculosis/HIV Coinfection

Updated: September 12, 2024
Reviewed: September 12, 2024

Key Considerations and Recommendations

• Treatment for latent tuberculosis infection (LTBI) in people with HIV should take into consideration the individual's antiretroviral (ARV) regimen as noted below.
  ○ General recommendations for **once-weekly** isoniazid plus rifapentine for 3 months (3HP) and **once-daily** isoniazid plus rifapentine for 1 month (1HP):
  ▪ These regimens **are not recommended** for people who require twice-daily dolutegravir (DTG) therapy (e.g., those with certain integrase strand transfer inhibitor [INSTI]–associated resistance substitutions or clinically suspected INSTI resistance) **(AIII).**
  ▪ Tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) **(AIII),** tenofovir alafenamide (TAF)/FTC **(BIII),** or abacavir (ABC)/lamivudine (3TC) **(BIII)** can be used as the nucleoside reverse transcriptase inhibitor (NRTI) backbone. Rifapentine may lower concentrations of TAF. If used, monitor for virologic response.
  ○ For 3HP
  ▪ Efavirenz (EFV) 600 mg once daily or raltegravir 400 mg twice daily can be used **(AII).**
  ▪ DTG 50 mg once daily may be used for those in whom once-daily DTG is appropriate **(BII).**
  ○ For 1HP
  ▪ EFV 600 mg once daily can be used without dose adjustment **(AI).**
  ▪ For a person with virologic suppression while on a DTG 50 mg once-daily regimen, the DTG dose should be increased to 50 mg twice daily throughout the course of 1HP, continuing DTG 50 mg twice daily for 14 days after 1HP completion before switching back to once-daily DTG dosing **(AII).**
  ○ With daily isoniazid alone for 6 or 9 months, any ARV regimen can be used **(AIII).**
  ○ If rifampin is used to treat LTBI, clinicians should review Tables 24a through 24g to assess the potential for drug–drug interactions between rifampin and different ARV drugs **(AII).**
• All people with HIV and active tuberculosis (TB) who are not on antiretroviral therapy (ART) should be started on ART **(AI)** as described below.
  ○ **CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI).**
  ○ **CD4 counts ≥50 cells/mm^3:** Initiate ART within 2 to 8 weeks of starting TB treatment **(AI).**
  ○ **During pregnancy, regardless of CD4 count:** Initiate ART as early as feasible for treatment of the person with HIV and prevention of HIV transmission to the infant **(AIII).**
  ○ **With TB meningitis:** Initiate ART after TB meningitis is under control and after at least 2 weeks of anti-TB treatment to reduce the risk of life-threatening inflammation in a closed space as a result of immune reconstitution **(AIII).**
• For people with active TB who are receiving ART, the ARV regimen should be assessed with particular attention to potential drug–drug interactions between ARVs and TB drugs. Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), in particular, have considerable potential for drug–drug interactions. The ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 24a through 24g for drug interaction data and dosing recommendations) **(AII).**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Managing Latent Tuberculosis Infection in People With HIV

Approximately one-quarter of the world's population has tuberculosis (TB) infection, with a 5% to 10% lifetime risk of progressing to active disease.[1] Among individuals with latent TB infection (LTBI), the risk of developing active TB is much higher among those who also have HIV, and this risk increases as immune deficiency worsens.[2]

Tuberculosis Preventive Treatment

After active TB has been excluded, the Centers for Disease Control and Prevention preferentially recommends one of the following short-course regimens for LTBI treatment (see Treatment Regimens for Latent TB Infection):

- 3 months of once-weekly isoniazid plus rifapentine (3HP)
- 4 months of daily rifampin (4R)
- 3 months of daily isoniazid plus rifampin (3HR)

The World Health Organization (WHO)[3] and the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV also recommend 1 month of daily isoniazid with rifapentine (1HP) as an alternative short-course regimen.

For more than 30 years, isoniazid had been the cornerstone of treatment for LTBI to prevent active TB. Randomized controlled clinical trials have demonstrated that treatment with isoniazid for 6 or 9 months for LTBI in people with HIV reduces the risk of active TB, especially in those with a positive tuberculin skin test.[4] Isoniazid given daily or twice weekly for 6 or 9 months can be coadministered with any antiretroviral (ARV) regimen and remains an alternative option, especially for people in whom rifamycin antibiotics cannot be used **(AIII).**

In the PREVENT TB study, the combination of isoniazid and rifapentine administered once a week for 3 months (3HP), as directly observed therapy, was as safe and effective as 9 months of isoniazid in preventing TB in people with HIV who were not on antiretroviral therapy (ART).[5] Another study randomized 1,148 South African adults with HIV who were not on ART to one of four treatment groups: 3 months of isoniazid and rifapentine, 3 months of isoniazid and rifampin, 6 months of isoniazid, or isoniazid continued for the duration of the trial. TB incidence did not differ among the groups.[6] The Panel for the Use of Antiretroviral Agents in Adults and Adolescents With HIV (the Panel) recommends dolutegravir (DTG) 50 mg once daily with 3 months of once-weekly isoniazid and rifapentine in people with virologic suppression and for whom once-daily DTG is appropriate **(BII).** More importantly, this 3-month regimen **is not recommended** for people who require twice-daily DTG therapy (e.g., those with certain integrase strand transfer inhibitors [INSTI]–associated resistance substitutions or clinically suspected INSTI resistance) **(AIII).** Isoniazid given daily for 6 or 9 months should be used in this setting.

A study of 6,000 people that compared completion rates, safety, and effectiveness of 4 months of daily rifampin (4R) versus 9 months of isoniazid found that 4R was non-inferior to isoniazid for 9 months for the prevention of TB disease, and that safety and completion rates were superior for 4R.[7] However, this trial included only 242 (4%) participants with HIV. While 4R may also be considered for TB-preventive treatment, clinicians should pay careful attention to potential drug–drug interactions with specific ARV drugs (see Tables 24a through 24g).

In 3,000 people with HIV infection in the BRIEF TB study, no difference was observed in TB incidence between those who received 1HP and those who received 9 months of isoniazid.[8] Approximately half of the participants were on ART (either efavirenz [EFV] or nevirapine-based regimens) while receiving the 1-month regimen. Fewer adverse events and a higher treatment completion rate occurred with the 1HP regimen than with 9 months of isoniazid.

Although rifapentine induces cytochrome P450 (CYP) isoenzymes and can potentially cause significant drug–drug interactions with ARVs, pharmacokinetic (PK) data support its use daily **(AI)** or once weekly **(AII)** with EFV 600 mg daily,[9,10] and once weekly with raltegravir (RAL) 400 mg twice daily **(AII).**[11] In a Phase 1/2 study of 60 adults with HIV and virologic suppression on once-daily dolutegravir (DTG)-based ART and weekly rifapentine with isoniazid,[12] DTG trough concentrations were reduced by 50% to 60%; all but one participant's trough concentration remained above the DTG protein-adjusted 90% inhibitory concentration (IC_{90}), and all HIV viral loads remained suppressed. In a multicenter PK study (A5372), 32 adults with HIV and virologic suppression on DTG-containing ART received DTG 50 mg twice daily throughout the course of 1HP and for 14 days after.[13] DTG trough concentrations were comparable with standard-dose DTG once daily without 1HP, and 31 (96.9%) of 32 participants maintained virologic suppression. One participant had an HIV RNA of 160 copies/mL at Day 28, with HIV RNA <50 copies/mL upon repeat testing on Day 42. Based on these data, the Panel recommends DTG 50 mg twice daily when given with 1HP in people with virologic suppression, continuing DTG 50 mg twice daily for 14 days after 1HP completion before switching back to once-daily DTG dosing **(AII).**

When prescribing either 1HP or 3HP, tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) **(AIII),** tenofovir alafenamide (TAF)/FTC **(BIII),** or abacavir (ABC)/lamivudine (3TC) **(BIII)** can be used as the nucleoside reverse transcriptase inhibitor (NRTI) backbone. The drug concentrations for ABC, TDF, 3TC, and FTC are not expected to be affected by rifapentine. Rifapentine may lower concentrations of TAF; if TAF is used, monitor for virologic response.

If a person with HIV has been in close contact with a person with drug-resistant TB, the options for LTBI treatment should be modified, taking into consideration drug-susceptibility test results from the source patient. In this setting, consultation with a TB expert is advised.

Isoniazid Preventive Therapy Plus Antiretroviral Therapy in Pregnant People With HIV

A randomized trial of isoniazid preventive therapy (IPT) compared isoniazid initiated during pregnancy (immediate IPT) to isoniazid delayed until 12 weeks postpartum (deferred IPT) in 956 women with HIV on ART. A greater number of adverse pregnancy outcomes were seen in women on immediate IPT, suggesting that IPT should be delayed until after delivery.[14] Treatment-related maternal adverse events were higher than expected in both arms. In the BRIEF TB study, first-trimester IPT exposure was associated with a nearly twofold increased risk of fetal demise—mostly spontaneous abortion—though the association was attenuated when adjusted for covariates proximal to pregnancy outcome, including ART use.[15] However, two observational studies from South Africa showed better pregnancy outcomes and no increase in hepatotoxicity in pregnant women on ART receiving antenatal IPT.[16,17] The WHO continues to recommend IPT for individuals with HIV.[3]

Impact of Antiretroviral Therapy in Preventing Active Tuberculosis

Effective ART can prevent active TB in areas with high TB prevalence. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV to one of four study arms: deferred ART, deferred ART plus IPT, early ART, or early ART plus IPT. The initial results

demonstrated that IPT and early ART each independently reduced the risk of a serious HIV-related event, many of which were TB, and that IPT with early ART provided the best protection from serious HIV events and death.[18] Data from longer follow-up (median 4.9 years) showed that 6 months of IPT given early in the course of HIV infection provided a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART.[19] In the START study, 4,685 participants with CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3 were randomized to receive immediate ART or deferred ART. For participants in the deferred ART arm, ART was started when their CD4 count dropped to 350 cells/mm^3 or if they developed a clinical condition that required ART. TB was one of the three most common clinical events, occurring in 14% of participants in the immediate ART group and 20% of participants in the deferred ART group.[20] Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with a high prevalence of TB/HIV coinfection.

Antiretroviral Therapy for People With HIV and Active Tuberculosis

All people with HIV/TB disease should be treated with ART **(AI)**, although the timing of ART initiation may vary as discussed below. Important considerations related to the use of ART in people with active TB disease include the following:

- When to start ART in the setting of drug-resistant TB and in people with TB meningitis,
- Significant PK drug–drug interactions between anti-TB and ARV drugs, *and*
- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in people with HIV should follow the general principles guiding treatment for people without HIV. The Adult and Adolescent Opportunistic Infection Guidelines include a more complete discussion of the diagnosis and treatment of TB disease in people with HIV.

The TB Trials Consortium Study 31/ AIDS Clinical Trials Group (ACTG) A5349 demonstrated success with a shorter, 4-month regimen.[21] This randomized, open-label, controlled Phase 3 trial compared two 4-month rifapentine-containing regimens to the standard 6-month control regimen of isoniazid plus rifampin. In 2,516 participants, including 193 (8%) with HIV, the rifapentine-moxifloxacin regimen was non-inferior to the control regimen, with 11.6% versus 9.6% unfavorable outcomes, respectively (difference 2.0%; 95% confidence interval, −1.1% to +5.1%), and it was safe and well tolerated. Participants with HIV were either already on an EFV-based ART or initiating an EFV-based ART.[22] In both groups, EFV concentrations were decreased slightly, but most maintained EFV concentrations of >1 mg/L and undetectable viremia.[23] This 4-month TB regimen with DTG-based ART is currently under investigation in the ACTG A5406 trial (NCT05630872).

Tuberculosis Diagnosed While a Person Is Receiving Antiretroviral Therapy

ART should be continued when TB is diagnosed in a person receiving ART, but the ARV regimen should be assessed with particular attention to potential drug interactions between ARVs and TB drugs (discussed below). The person's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen **(AII)** (see Tables 24a through 24g for dosing recommendations).

Tuberculosis Diagnosed in a Person With HIV Not Yet Receiving Antiretroviral Therapy

ART should not be delayed until TB treatment is completed, because this strategy was associated with higher mortality rates in the SAPiT-1 study.[24] The timing of ART in specific populations is discussed below.

People with HIV and CD4 counts <50 cells/mm^3: Three large randomized clinical trials in people with HIV/TB disease, conducted in Africa and Asia, all convincingly showed that early ART in those with CD4 counts <50 cell/mm^3 significantly reduced AIDS events or deaths.[25-27] In these studies, early ART was defined as either ≤2 weeks[26] or ≤4 weeks[25] after initiation of TB therapy.

Collectively these three trials support the initiation of ART within the first 2 weeks of TB treatment in people with CD4 counts <50 cells/mm^3 **(AI).**

People with HIV and CD4 counts ≥50 cells/mm^3: In two of the three studies mentioned above,[26,27] no survival benefit was seen for people with CD4 counts ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8–12 weeks), after beginning TB treatment. Importantly, none of the studies demonstrated harm from earlier ART initiation, and many benefits of ART in people with HIV are well documented, regardless of TB coinfection. It is unlikely that more trials will be conducted to specifically inform the decision on when to start ART in people with TB and CD4 counts ≥50 cells/mm^3.

However, given the growing body of evidence supporting early ART in general and the lack of data showing any harm in people with TB coinfection, the Panel recommends ART initiation within 2 to 8 weeks after starting TB treatment for people with CD4 counts ≥50 cells/mm^3 **(AI).**

People with HIV and drug-resistant TB: People may have single-drug-resistant TB, multidrug-resistant TB (MDR-TB) (defined as strains with resistance to both isoniazid and rifampin); pre-extensively drug-resistant (pre-XDR) TB (defined as MDR-TB plus resistance to any fluoroquinolone), or extensively drug-resistant TB (XDR-TB) (defined as MDR-TB plus resistance to any fluoroquinolone and at least one additional Group A drug listed in the WHO guidelines).[28] Historically, mortality rates in people with MDR-TB or XDR-TB and HIV have been high,[29] but more recent data suggest that treatment outcomes are similar for people with MDR-TB with and without HIV infection. In the Nix-TB study of an all-oral, 6-month regimen of bedaquiline, pretomanid, and linezolid for MDR-TB and XDR-TB, 51% of the 109 participants also had HIV. Rates of cure, serious adverse events, and mortality were similar among those with and without HIV.[30]

Although randomized clinical trial data to guide the optimal timing for ART initiation are lacking, the WHO guidelines recommend ART for all people with HIV and drug-resistant TB, irrespective of CD4 count, as early as possible (within the first 8 weeks), following the initiation of TB treatment.

Management of people with HIV and drug-resistant TB is complex, and expert consultation is advised **(AIII).**

People with TB meningitis: TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, people with HIV-associated TB meningitis were randomized to immediate ART or to ART deferred until 2 months after initiation of TB treatment. A significantly higher rate of severe (Grade 4) adverse events was seen in people who received immediate ART than in those who received deferred ART (80.3% vs. 69.1% for immediate and deferred ART, respectively; $P = 0.04$).[31]

Despite these study results, in the setting of TB meningitis, many experts would recommend initiating ART early in settings where close monitoring of drug-related toxicities and central nervous system adverse events is feasible (see Adult and Adolescent Opportunistic Infection Guidelines) **(BIII).** ART should be started after TB meningitis is under control and after at least 2 weeks of anti-TB treatment to reduce the risk of life-threatening inflammation in a closed space as a result of immune reconstitution **(AIII).**

Managing people with HIV and TB meningitis is complex, and expert consultation is advised **(AIII).**

Pregnant people: All people with HIV and active TB who are pregnant should be started on ART as early as feasible, both for the treatment of the person with HIV and prevention of HIV transmission to the infant **(AIII).** The choice of ART should be based on efficacy and safety in pregnancy and should take into account potential drug–drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).

Drug Interaction Considerations

Rifamycin antibiotics (rifabutin, rifampin, and rifapentine) are an important component of TB treatment regimens because of their sterilizing ability. However, they are associated with a considerable potential for drug interactions due to their ability to affect various drug-metabolizing enzymes and transporters. Rifampin is a potent inducer of the CYP (mostly 3A and 2C subfamilies) enzyme system, P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Rifabutin and rifapentine are both substrates and inducers of CYP3A4. As potent inducers of metabolic enzymes and drug transporters, rifamycin-related drug interactions may result in significant reduction in ARV drug exposure. The ARV drugs most affected include all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), INSTIs, the CCR5 antagonist maraviroc (MVC), the gp120 attachment inhibitor fostemsavir, and the capsid inhibitor lenacapavir. Coadministration of rifamycins with long-acting injectable cabotegravir with rilpivirine or lenacapavir is contraindicated.[32] Most NRTIs, the fusion inhibitor enfuvirtide, and the CD4 post-attachment inhibitor ibalizumab are not expected to have significant drug interactions with the rifamycins. Tables 24a through 24g outline the magnitude of these interactions and provide dosing recommendations when rifamycin antibiotics and selected ARV drugs are used concomitantly.

Because TAF is a P-gp substrate, its plasma concentrations may be reduced by rifamycin antibiotics. Current labeling does not recommend concomitant administration of TAF and any rifamycin antibiotic.[33] However, in a healthy volunteer study, following administration of TAF/FTC with rifampin, intracellular tenofovir-diphosphate concentrations were still 4.2-fold higher than those achieved by TDF.[34] TAF can be used with rifampin with caution and close monitoring of virologic response.

Several ARV drugs are not recommended for use with rifampin; clinicians should refer to Tables 24a through 24g before prescribing these drugs in combination. When DTG, RAL, or MVC are used with rifampin for TB treatment, the ARV doses must be increased. In contrast to its effect on other ARV drugs, rifampin leads to only a modest reduction in EFV concentrations.[35,36] Even though the current EFV label recommends increasing the EFV dose from 600 mg once daily to 800 mg once daily in people weighing >50 kg,[37] this dosage increase is generally not necessary. The Panel recommends EFV 600 mg for individuals receiving rifampin therapy. High-dose (up to 35 mg/kg/day) rifampin is currently being evaluated for treatment of TB meningitis. The data on the magnitude and extent of interactions between high-dose rifampin and ARV drugs are limited.[38-40]

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin for TB treatment, especially in people taking PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 24a through 24g for dosing recommendations).

Rifapentine is a long-acting rifamycin that may be given once weekly or once daily. When given daily, it is a more potent inducer than rifampin.[41] Once-daily rifapentine did not affect the oral clearance of EFV 600 mg in individuals with HIV in the BRIEF TB study,[42] and once-weekly rifapentine has demonstrated minimal impact on EFV 600 mg exposure.[9] Once-weekly rifapentine led to an increase, rather than a decrease, in RAL drug exposure in healthy volunteers.[11] A PK study conducted in South Africa found that once-weekly isoniazid-rifapentine plus once-daily DTG was well tolerated in participants with HIV, with only 3 of 60 participants experiencing a Grade 3 adverse effect (two with elevated creatinine and one with hypertension). The extent of the interaction varied by day, with a 23% reduction on Day 1, 64% reduction on Day 2, and 56% reduction on Days 5 and 6 after isoniazid-rifapentine dose.[12] In a multicenter PK study (A5372), 32 adults with HIV and virologic suppression on DTG-containing ART received DTG 50 mg twice daily during 1HP and for 14 days after.[13] DTG trough concentrations were comparable with standard-dose DTG once daily without 1HP.

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections, such as TB, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). Manifestations of unmasking TB-associated IRIS (TB-IRIS) are characterized by their marked inflammatory nature, such as high fever, respiratory distress, lymphadenitis, abscesses, and sepsis syndrome. Manifestations of paradoxical TB-IRIS include fevers, new or worsening lymphadenopathy, new or worsening pulmonary infiltrates, enlarging pleural effusions, and new or enlarging tuberculomas.

TB-IRIS has been reported in 8% to more than 40% of people who start ART after being diagnosed with TB, although the incidence depends on the definition of IRIS and the intensity of monitoring.[43,44] IRIS is infrequently associated with mortality.

Predictors of IRIS include a baseline CD4 count <50 cells/mm^3; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and <30-day interval between initiation of TB and HIV treatments.[45] Most IRIS in HIV/TB disease occurs ≤3 months from the start of ART.

In general, the Panel recommends continuing ART without interruption during IRIS **(AIII).**

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Limitations to Treatment Safety and Efficacy

Adherence to the Continuum of Care

Updated: September 12, 2024
Reviewed: September 12, 2024

Key Considerations and Recommendations

• Linkage to HIV care and adherence to both antiretroviral therapy (ART) and clinic appointments should be regularly assessed.
• An individual's barriers to ART and clinic appointment adherence should be assessed before or shortly after the initiation of ART and regularly thereafter.
• Rapid access to ART is one of the pillars of the United States' plan to end the HIV epidemic; therefore, delays in access to ART should be addressed and treatment initiated as soon as possible.
• People with HIV having ART adherence problems should be placed on regimens with high genetic barriers to resistance, such as dolutegravir, bictegravir, or boosted darunavir. Side effects, out-of-pocket costs, convenience, and individual preferences should also be considered.
• People with HIV having difficulties with adherence to appointments or ART should be provided additional adherence support using a constructive, collaborative, nonjudgmental, and problem-solving approach.
• The approach taken to improve adherence should be tailored to each person's needs and barriers to care. Approaches could include, but are not limited to—
  ○ Changing ART to simplify dosing or to reduce side effects
  ○ Allowing flexible appointment scheduling
  ○ Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments
  ○ Linkage to resources to assist with unmet social and economic needs, such as transportation, food, housing, and other support services
  ○ Linkage to services to overcome stigma, substance use, or mental illness
• A multidisciplinary approach—including collaborations with nursing, pharmacy, social work, and case management (to the extent available—is often necessary to identify solutions to ART and appointment adherence. The clinician's role is to help people with HIV understand the importance of adherence to the continuum of care, identify the barriers to adherence and address those that are within their purview, and link them to resources to overcome other barriers.
• Single-tablet ART regimens are generally recommended when clinically appropriate, but high-quality evidence to definitively recommend them is lacking and shared decision-making between clinicians and people with HIV is essential **(BIII).**
• At this time, evidence does not support the use of financial incentives to engage people with HIV in ongoing routine care.
• Methods to estimate adherence based on drug levels measured in plasma, dried blood spots, urine, and hair samples are available. Measuring adherence with these methods has not been shown in randomized studies to improve outcomes. However, these methods should be used in a collaborative manner to avoid an adversarial relationship between the provider and people with HIV.
• Because delayed administration of long-acting cabotegravir plus rilpivirine (LA CAB/RPV) may lead to the emergence of drug resistance, LA CAB/RPV is not generally recommended as a complete regimen in people with viremia due to suboptimal adherence to ART, or in people who have ongoing challenges with retention in HIV care. However, based on very limited data, the Panel for the Use of Antiretroviral Agents in Adults and Adolescents With HIV recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, and who have no evidence of resistance to rilpivirine RPV or CAB and, with shared decision-making between providers and people with HIV **(CIII).** See Virologic Failure for a more detailed discussion.

- A summary of best practice interventions to improve linkage, retention, and adherence can be found in the Centers for Disease Control and Prevention's Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention.

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

HIV treatment adherence includes initiating care with an HIV provider (linkage to care), regularly engaging in appointments (retention in care), and adhering to antiretroviral therapy (ART). The concept of a "continuum of care" has been used to describe the process of HIV testing, linkage to HIV care, initiation of ART, adherence to ART, retention in care, and virologic suppression.[1-3] The Centers for Disease Control and Prevention (CDC) estimates that about 13% of people with HIV are undiagnosed in the United States.[4] Based on 2022 data, about 82% of individuals were linked to care within 30 days of receiving an HIV diagnosis.[5,6] However, only 54% of people with diagnosed HIV were retained in HIV care. It is estimated that only approximately 69% of people with complete data were virologically suppressed within 6 months of diagnosis. This low rate of viral suppression is primarily due to poor adherence to clinic appointments and ART.[5,7] Outcomes along the continuum of care also vary by geographic region and other population characteristics, such as sex, race and ethnicity, and HIV risk factors.[7] To achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, adherence to each step in the continuum of care is critical.[8] It is important to note that retention and adherence may fluctuate as a result of life events, changes in insurance status, comorbid conditions, and health system changes, causing people with HIV to shift back and forth on the continuum. Knowledgeable providers and high-quality system processes are vital in promoting rapid linkage and sustained retention in care and adherence to ART. Finally, clinicians should recognize that adherence is a complex behavior requiring knowledge, motivation, memory, behavior change, external resources, and successful and persistent interaction with complex and, sometimes, challenging health care systems.[9-11] The patient–provider relationship is central to improving HIV care engagement and adherence to treatment. Providers must recognize that adherence is a collaborative effort between clinicians and people with HIV.

Addressing social determinants of health (SDOH) is critical to adherence along the HIV continuum of care. The CDC defines SDOH as "the conditions in which people are born, grow, work, live, and age" and "that influence health outcomes."[12] SDOH include access to education, income, nutritious food, transportation, stable housing, and health insurance coverage, as well as policies that may lead to structural racism, HIV criminalization, and stigma related to sexual and gender minority identification or immigration status. There are several commonly used screening tools for health-related social needs, including the Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences (PRAPARE),[13] the American Academy of Family Physicians Social Needs Screening Tool (long and short forms),[14,15] and the Centers for Medicare & Medicaid Services (CMS) Accountable Health Communities Health-Related Social Needs (AHC-HRSN) Screening Tool.[16] The CMS Accountable Health Communities Model conducted a randomized trial connecting beneficiaries to community resources for five core health-related social needs compared with a referral-only group. Individuals in the community resources group received an in-depth assessment of social needs, planning, referral to community services, and follow-up until the needs were resolved or determined unresolvable. The beneficiaries who received community service navigation experienced reduced emergency department visits and a trend toward lower expenditures and improved hospital-based utilization outcomes compared with the referral-only group.[17] Any unmet

social and economic needs identified via screening should be addressed, either through direct service provision or by community referrals.

This section provides guidance on linking people with HIV to care, assessing and improving retention in care, and assessing and improving adherence to ART. The CDC maintains a Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention to improve linkage, retention, and adherence, and the Health Resources and Services Administration (HRSA) has multiple tools to assist clinics housed in the Ryan White HIV/AIDS Program (RWHAP) Best Practices Compilation. In addition, a number of other groups and organizations have provided guidance for improving adherence to the steps in the care continuum.[8,18]

Linkage to Care

Receiving an HIV diagnosis can be traumatic, and linkage to care efforts must be delivered with compassion and persistence. The time from diagnosis to linkage to care can be affected by many factors, including insufficient socioeconomic resources, active substance use, mental health problems, stigma, and disease severity (symptomatic HIV is associated with more successful linkage).[19-23] In the United States, youth, people who use injection drugs, and Black/African American people have lower rates of linkage to care.[7] Some health system factors have also been associated with linkage success or failure. Co-location of testing and treatment services[22] and active linkage services (e.g., assistance in setting up HIV care appointments, maintaining an active relationship with individuals until linkage is completed, providing linkage case management services)[24-26] bolster linkage to care. Conversely, passive linkage (e.g., only providing names and contact information for treatment centers) is associated with lower linkage to care.

Monitoring Linkage to Care

Linking to HIV care after a new HIV diagnosis is defined as completing an outpatient appointment with a clinical provider who has the skills and ability to treat HIV, including prescribing ART. People with HIV should be linked to care as soon as possible after HIV diagnosis, preferably within 30 days. Monitoring linkage is critical to ensure that interventions can effectively reach people who are not linked to care. If the facilities that diagnose and treat an individual are the same or share the same electronic medical record system, it is relatively straightforward to monitor linkage to care. Monitoring linkage for people whose HIV is diagnosed outside the treatment provider's health care system is difficult and generally is the responsibility of the diagnosing provider or entity and the public health authority. However, once people with HIV make contact with the treating clinical system, they should be engaged in linkage efforts. The referring entity should monitor for successful linkage to and retention in HIV care.

Improving Linkage to Care

Strategies to improve linkage to care are summarized in Table 19 below. Linkage efforts should include immediate referral to care at diagnosis, appointment reminders, and outreach efforts if needed.[24] The only intervention shown to increase linkage to care in a randomized trial conducted in the United States is the Anti-Retroviral Treatment and Access to Services (ARTAS) intervention.[25] In this study, participants randomized to the control arm received information about HIV and care resources and a referral to a local HIV medical provider, whereas participants in the intervention arm worked with an ARTAS interventionist for five sessions, 90 days, or until linkage—whichever came first. The interventionist helped participants to identify and use their strengths, abilities, and skills to

link to HIV care; participants were also linked to community resources. Linkage to care, defined in this study as completing at least one visit with an HIV clinician within the first 6 months, was greater among the ARTAS participants than the control participants (78% vs. 60%, adjusted risk ratio = 1.36, $P < 0.001$). Furthermore, a greater percentage of ARTAS participants were retained in care, defined as visiting an HIV clinician at least once in each of the first two 6-month blocks after enrollment (64% vs. 49% for ARTAS and control participants, respectively; adjusted risk ratio = 1.41, $P = 0.006$). The results from the ARTAS intervention have been replicated in a community-based study.[26] The CDC supports free training in the ARTAS intervention. Other studies support the importance of post-test counseling to educate, motivate, and present positive messages about HIV,[27] peer support,[28] and engaging people with HIV at the clinic in advance of the visit with the provider.[29] Financial incentives did not increase linkage to care within 90 days in a large randomized trial.[30]

Retention in Care

Poor retention in HIV care is associated with a greater risk of death.[31,32] Poor retention is more common in people who use substances, have serious mental health problems, have unmet socioeconomic needs (e.g., housing, food, transportation), lack financial resources or health insurance, have schedules that complicate adherence, have been recently incarcerated, or face stigma.[33-36] At the provider and health system level, low trust in providers and a poor relationship between providers and people with HIV have been associated with lower retention, as has lower satisfaction with the clinic experience.[37-39] Availability of appointments and timeliness of appointments (i.e., long delay between the appointment request and the appointment date) and scheduling convenience are also factors.

Monitoring Retention in Care

Retention in care should be routinely monitored.[8] There are various ways to measure retention, including measures based on attended visits over a defined period of time (constancy measures) and measures based on missed visits.[40] Both approaches are valid and independently predict survival.[41] Missed visits and a prolonged time since the last visit are relatively easy to measure and should trigger efforts to retain or reengage a person in care. Constancy measures (e.g., at least two visits that are at least 90 days apart over 1 year, or at least one visit every 6 months over the last 2 years) can be used as clinic quality assurance measures.

Improving Retention in Care

Strategies to improve retention in care are summarized in Table 19 below. The Retention through Enhanced Personal Contact (REPC) intervention was tested in a randomized trial in six clinics in the United States. The study enrolled people with HIV who had a history of inconsistent clinic attendance. The intervention relied on personal contact and included a brief face-to-face meeting upon returning to care and at each subsequent clinic visit, plus three types of phone calls (check-ins between visits, to provide appointment reminders just before visits, and to attempt to reschedule missed visits). REPC resulted in small but significant improvements in retention in care, including in racial/ethnic minority populations and people with detectable plasma HIV RNA.[42] When necessary, in-clinic opioid replacement therapy helps opioid users remain in care.[43] An intervention using the electronic medical record to alert providers when people had suboptimal follow-up or high viral loads also improved retention in care.[44]

Telehealth has emerged as an important modality for retention in HIV care during the COVID-19 pandemic. A cluster-randomized study conducted in the U.S. Department of Veterans Affairs health facilities before the pandemic showed that the availability of telehealth resulted in improvements in viral suppression and the number of completed visits.[45] Reengaging and retaining people who are out of care remains particularly challenging.

Navigation services for out-of-care individuals with HIV in a New York City Medicaid health plan resulted in faster re-linkage to care but did not improve retention in care.[46] In two randomized trials involving out-of-care, hospitalized people with HIV, peer counselors and patient navigators did not improve re-linkage to care after hospital discharge.[47,48] Two randomized studies tested a Data to Care intervention, which uses clinic and public health data to reach and reengage out-of-care people with HIV.[49] One trial conducted in Seattle found that the intervention did not result in significantly faster time to re-linkage or viral suppression.[50] However, only people with unsuppressed viremia and CD4 T lymphocyte (CD4) cell counts <350 cells/mm^3 or people with no laboratory values in the preceding 12 months were included, reflecting the HIV treatment guidelines at the time. The Cooperative Re-Engagement Controlled Trial (CoRECT) was more recently conducted in the Northeast United States (Connecticut, Massachusetts, Philadelphia) and included people with HIV with no evidence of a clinic visit or laboratory measurement in the preceding 6 months, regardless of their most recent laboratory results. The proportion of people re-linked to care within 90 days and retained in care at 12 months was significantly higher in the intervention group, but no differences were observed in the proportion who achieved viral suppression in 12 months. Time to viral suppression among those who achieved viral suppression in 12 months was shorter for participants who were randomized to the Data to Care arm compared with the standard of care. Using the Data to Care approach requires substantial resources and notable privacy concerns; although short-term re-linkage may be improved, there is no evidence of an impact on long-term re-linkage or time to viral suppression.

Data from nonrandomized studies are less conclusive, but many interventions bear mentioning. Clinic-wide marketing (e.g., posters, brochures) and customer service training of staff to promote attending scheduled visits and provide people with a welcoming and courteous experience have improved retention.[51] People with HIV who rated their experience with their doctor more highly were more likely to stay in care.[52] Stepped-case management and social and outreach services,[53] including mobile health applications that enhance communication and provide support, are beneficial, although the applications that have been developed and studied are not available for widespread public use. Differentiated care approaches reduce the need for appointments and other expectations for people doing well and allow extra resources to be devoted to people not achieving optimal health outcomes. The evidence to support the use of differentiated care is strongest in low-resource settings, whereas in the United States, the evidence is limited to observational data, which suggests the approach has a beneficial impact.[54]

Overall, these data support the concept that all clinic personnel, from the facilities' staff to nurses to providers, play important roles in supporting retention in care by providing the optimal care experiences, constructively affirming attendance rather than criticizing non-attendance, and collaboratively solving problems with people to overcome barriers to care.[38,42,51] Flexible appointment schedules, expanded clinic hours, and copay or other financial or insurance assistance—such as that provided by the RWHAP—also facilitate uninterrupted access to clinical care. Navigation services, telehealth, and engaging with people through mobile health applications are likely to improve outcomes, although the evidence is not sufficient to support their use unequivocally.

The use of financial incentives or rewards to promote retention in care has been studied. A large study randomized clinic sites to financial incentives or standard of care. At baseline, 45% of the participants were retained in care in these clinics. The relative increase in the proportion of participants retained in care was 9% higher in clinics offering incentives than in standard-of-care clinics. Viral suppression also improved by 4% at financial incentive clinics, from a baseline of 62%.[30] Evidence from a *post hoc* analysis of a subset of the sites involved in that trial shows a reduced but persistent improvement in retention in care after the withdrawal of the incentives without a persistent effect on viral suppression.[55] In another large, randomized study of people who were out of care and hospitalized, financial incentives plus patient navigation did not lead to sustained improvement in retention or viral load suppression compared to standard care.[47] At this time, financial incentives remain experimental in the context of improved retention due to a lack of data supporting their use in routine care.

Adherence to Antiretroviral Therapy

Adherence to ART can be influenced by several factors, including a person's social situation, clinical condition, the prescribed regimen, and the patient–provider relationship.[56] Poor adherence is often a consequence of one or more behavioral, structural, and psychosocial barriers (e.g., depression and other mental illnesses, neurocognitive impairment, low health literacy, low levels of social support, stressful life events, busy or unstructured daily routines, active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, inconsistent access to medications due to financial and insurance status).[57-60]

Characteristics of one or more components of the prescribed regimen can affect adherence. Once-daily regimens,[61] including those with low pill burden (even if not one pill once daily), no food requirement, and few side effects or toxicities, are associated with higher levels of adherence.[62,63] Single-tablet regimens (STRs) that include all antiretroviral (ARV) drugs in one pill taken once daily are easier for people to use. However, data to support or refute the superiority of an STR versus a once-daily multi-tablet regimen (MTR), as might be required for the use of some generic-based ARV regimens, are limited. Comparisons of these regimens are hampered because not all drugs and classes are available as STRs. There are demonstrated beneficial effects on virologic suppression in a meta-analysis of MTRs versus STRs.[64,65] Whether an STR is beneficial in people with HIV who are ART-naive is not known, with observational cohort studies showing the benefit of a once-daily STR versus a once-daily MTR.[63,66-69] On the other hand, observational data from Spain showed that co-formulated dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) resulted in similar viral suppression compared to DTG plus ABC/3TC when used both at treatment initiation and when people with viral suppression on STR were switched to the two-pill formulation as a cost-saving strategy.[70] Given these findings and their wide availability, STRs are generally recommended when clinically appropriate, but high-quality evidence to definitively recommend them is lacking, and shared decision-making is essential **(BIII).**

Characteristics of the clinical setting can also have important structural influences on the success or failure of medication adherence. Settings that provide comprehensive multidisciplinary care (e.g., by case managers, pharmacists, social workers, mental health and substance use providers) support the complex needs of individuals, including those related to medication adherence. Treatment programs for substance use may offer services that promote adherence, such as directly observed therapy (DOT) (see Substance Use Disorders and HIV).

Monitoring Adherence to Antiretroviral Therapy

Adherence to ART should be assessed and addressed in a constructive and nonjudgmental manner at every clinic visit. Given the potency of contemporary ART, a detectable viral load identified during chronic care for a person with stable access to ART is most likely the result of poor adherence. Self-report, the most frequently used method for evaluating medication adherence, remains a useful tool. Carefully assessed self-report of high-level adherence to ART has been associated with favorable viral load responses,[71-73] whereas admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self-reporting often depends on how the clinician elicits the information. It is most reliable when ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses. To allow people to disclose lapses in adherence, some experts suggest inquiring about the number of missed doses during a defined period. For example, for a person with a detectable viral load, a provider might state, "I know it is difficult to take medicine every day. Most people miss doses at least sometimes. Thinking about the last 2 weeks, how many times have you missed doses? Please give me a rough estimate so I can help you take the best care of yourself." Other research supports simply asking people to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale[74,75] or using qualitative response categories.[73]

Other measures of adherence include pharmacy records and pill counts. Pharmacy records can be valuable when medications are obtained exclusively from a single source. Because pill counts can be altered, are labor intensive, and can be perceived as confrontational, they are generally not used in routine care. Electronic measurement devices are costly and are generally reserved for research settings. Finally, methods to estimate adherence based on drug levels measured in plasma, dried blood spots, urine, and hair samples are available.[76] Some of these are commercially available, but none have been shown in randomized studies to improve outcomes. However, if these methods are used, they should be implemented collaboratively between the provider and the person with HIV to avoid an adversarial relationship.

Improving Adherence to Antiretroviral Therapy

Strategies to improve adherence to ART are summarized in Table 19 below. Just as they support retention in care, all health care team members play integral roles in successful ART adherence programs.[72,77-79] An increasing number of interventions have proven effective in improving adherence to ART (for descriptions of the interventions, see the CDC's Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention). These interventions can be customized to suit a range of needs and settings. Many interventions that are efficacious in randomized trials require specialized training and resources before they can be implemented in routine care, and this has limited their impact. Nonetheless, these interventions have contributed to our knowledge in developing general principles of improving and maintaining adherence.

Every person with HIV must receive and understand basic information about HIV infection, including the goals of therapy (achieving and maintaining viral suppression, which will decrease HIV-associated complications and prevent transmission), the prescribed regimen (including dosing schedule and potential side effects), the importance of adherence to ART, and the potential for the development of drug resistance as a consequence of suboptimal adherence. People with HIV must also be positively motivated to initiate therapy, which can be assessed by simply asking people if they want to start treatment for HIV. Clinicians should assist people with HIV in identifying facilitating factors and potential barriers to adherence and develop multidisciplinary plans to attempt

to overcome those barriers. Processes for obtaining medications and refills should be clearly described. Transportation to pharmacy and clinic visits should be assessed with linkage to appropriate services as needed. Plans to ensure uninterrupted access to ART via insurance, copay assistance, pharmaceutical company assistance programs, or AIDS Drug Assistance Programs (ADAP), for example, should be made and reviewed with each person with HIV. Much of this effort to inform, motivate, and reduce barriers can be achieved by nonphysician members of the multidisciplinary team and can be accomplished concomitantly with, or even after, starting therapy.[80-83]

While delaying the initiation of ART is rarely indicated, some people may not be comfortable starting treatment right away. People expressing reluctance to initiate ART should be engaged to understand and overcome barriers to ART initiation. Although homelessness, substance use, and mental health problems are associated with poorer adherence, they are not predictive enough at the individual level to warrant withholding or delaying therapy given the simplicity, potency, and tolerability of contemporary ART. Rapid ART initiation at the time of HIV diagnosis has been pursued as a strategy to increase viral load suppression and retention in care, but safety data, data on intermediate or long-term outcomes, and data from randomized controlled trials conducted in high-resource settings are currently lacking.[80-86] In low-resource settings, data from randomized trials suggest that rapid ART probably increases ART use and viral suppression at 12 months, but data on other important outcomes—such as retention in care, regimen switching, and mortality—are not sufficient to draw conclusions.[87,88] Rapid access to ART has become a pillar of the United States' plan to end the HIV epidemic, and delays in access to ART should be addressed.[89] For more details, see Initiation of Antiretroviral Therapy.

Successful treatment requires a regimen that the individual can adhere to,[90,91] considering their daily schedule, tolerance of pills (number, size, and frequency), and any issues affecting absorption (e.g., use of acid-suppressing therapy, food requirements). As reviewed above, STRs have been associated with high rates of adherence. People with risk factors for poor adherence or a history of poor adherence should be offered regimens with high genetic barriers to resistance (e.g., a second-generation integrase strand transfer inhibitor [INSTI] or a boosted protease inhibitor), if clinically appropriate. Using shared decision-making, a medication choice and administration schedule should be tailored to each person's daily activities. Clinicians should explain to people that their first regimen is usually the best option for a simple regimen, which affords long-term treatment success. Establishing a trusting patient–provider relationship and maintaining good communication will help to improve adherence and long-term outcomes. Medication adherence can also be enhanced using medication reminder aids. The evidence is strongest for text messaging, although pillbox monitors, pill boxes, and alarms may also improve adherence.[92-96]

Positive reinforcement, such as informing people of their low or suppressed viral load and increased CD4 counts, can greatly help maintain high levels of adherence. Motivational interviewing has also been used with some success.[97-99] Other effective interventions include nurse home visits, a five-session group intervention, and couples- or family-based interventions. Interventions involving several approaches are generally more successful than single-strategy interventions, and interventions based on cognitive behavioral therapy and supporter interventions have been shown to improve viral suppression.[100] Problem-solving approaches that vary in intensity and culturally tailored approaches are also promising.[99,101,102] Providing additional therapy (e.g., for substance use or mental health) and social support may be important to maintain high levels of adherence. DOT has been effective in providing ART to people actively using drugs[103] but not to people in a general clinic population[104] or in home-based settings with partners responsible for DOT.[105,106] The use of incentives or rewards to

promote adherence has been studied, demonstrating improved adherence in one study conducted by the HIV Prevention Trials Network (HPTN)[30] and reduce viral load in another study that required very frequent viral load measurement and incentives.[107] Although the durability and feasibility of financial incentives are limited, and behavior change is generally not sustained after the incentives are withdrawn, the HPTN study did find some evidence of sustained adherence after 9 months.[55] Data are too limited to support the use of financial rewards for adherence to routine care.[47,108,109]

Transitions of Care

Transitions of HIV care are critical periods during which people may be more likely to fall out of care. Some important examples of transitions of care are discussed in further detail below.

Transition From Pediatric to Adult HIV Care

The transition from pediatric to adult HIV care requires proactive attention to the medical and psychosocial needs of adolescents as they move from a child-focused to an adult-focused health care system, with the goal of preventing disruption in care and ensuring ART adherence.[110] Recommendations for transition planning from pediatric to adult HIV care can be found in the Adolescents and Young Adults With HIV section of these guidelines and the Pediatric Antiretroviral Guidelines.

Transition From Obstetric to Primary HIV Care Postpartum

Pregnancy and the postpartum period offer a unique opportunity to engage in HIV care, both for people newly diagnosed with HIV during pregnancy and for people with HIV prior to pregnancy. Childcare responsibilities and postpartum depression can contribute to decreased adherence to HIV care in the postpartum period, thus requiring additional support services. Guidance on postpartum follow-up for people with HIV can be found in the Perinatal Guidelines.

Transitions Between Health Care Providers or Settings

Transitions in health care providers or settings can occur between hospitals, primary HIV care practices, ambulatory specialty care practices, long-term care facilities, home health, and rehabilitation facilities.[111] Safe transitions in HIV care can be supported by coordinating with HIV care providers and educating people with HIV and their support systems. In the setting of a health care facility discharge, bedside medication delivery or "Meds to Beds" programs may enhance post-discharge medication adherence by eliminating the need to visit a pharmacy to fill post-discharge medications.[112,113] In the setting of a residential move from one geographic area to another, a new HIV care provider would ideally be identified ahead of the move so that communication and transfer of medical records occur in a timely manner. This is particularly important for people with HIV who are receiving RWHAP services because not all HIV care providers receive RWHAP funding. HRSA provides an online resource for identifying RWHAP providers nationally. Provision of at least a 30-day ART supply at the time of a residential move may mitigate gaps in adherence due to delays in health care access in a new geographic area.

Reengagement in HIV Care After Loss to Follow-up

Adherence along the HIV care continuum is fluid and can change depending on an individual's life circumstances. In general, guidance around reengagement in care is similar to the guidance for

individuals who are newly diagnosed with HIV. However, specific attention should be paid to understanding the reasons for previous disengagement from care, and shared decision-making should be used to identify strategies to address these barriers using a multidisciplinary approach. Hospitalization can provide an important opportunity for reengagement when an acute illness may increase an individual's motivation for behavior change. As noted above, bedside medication delivery or "Meds to Beds" programs have the potential to enhance post-discharge medication adherence.[112,113]

Individuals in Custody Released From Jails and Prisons

HIV continues to disproportionately affect individuals who are incarcerated at a rate three times that of the general population. Approximately 1.1% of individuals in custody have HIV, compared with 0.4% of the general population.[114,115] Incarceration presents an opportunity to identify and treat previously undiagnosed people with HIV, reengage those who had fallen out of HIV care in the community before incarceration, and stabilize HIV treatment among those who struggled with adherence and retention in care in the community. HIV treatment inside carceral facilities should mirror treatment in the community with respect to ART selection. Treatment interruptions should be avoided when people enter and leave such facilities. HIV treatment outcomes can be improved by having HIV specialty care teams within carceral facilities to communicate and coordinate care with community-based providers. There are unique considerations when treating HIV inside prisons and jails, given a lack of individual privacy, restricted movement to the health care unit, HIV stigma, and solitary confinement—all of which can negatively impact ART adherence while in custody. Conversely, this setting can allow the individual in custody to focus on adherence and allow the health care team to assess the safety, tolerability, and effectiveness of an ART regimen.

Adherence challenges can increase exponentially upon release from custody and include lapses in medical and prescription benefits (including for mental health and substance use disorders), housing instability, lack of transportation, lack of identification and other important documents (e.g., birth certificate, social security card) needed to secure medical benefits, relapse to substance use, and risk of overdose. Interventions to reduce barriers to HIV treatment should be assessed during the prerelease discharge planning process when feasible and can be enhanced by accessing assistance through community-based organizations that provide post-release services.[116] Factors that promote treatment adherence post-release include registering for health insurance and completing an ADAP application prior to release,[117] coordinating follow-up HIV care with community providers, and providing a 30-day supply of ART at the time of release.[118] Various interventions to improve post-release treatment adherence have demonstrated the efficacy of an interdisciplinary medical team, including case management and patient navigation resources.[119-124]

Long-Acting Antiretroviral Therapy

An ART regimen of long-acting intramuscular cabotegravir and rilpivirine (LA CAB/RPV) given monthly or every 2 months has been studied and approved for use in populations with viral suppression. In addition, preliminary data from a randomized clinical trial suggest that LA CAB/RPV may be safe and effective among people without viral suppression despite intensive adherence support on oral ART; however, final data and long-term outcomes are not yet available.[125] The long pharmacologic tail of LA CAB/RPV after the last dose raises concerns about the emergence of drug-resistance mutations in people who discontinue therapy without rapidly transitioning to oral therapy. Further, efficacy data from randomized clinical trials do not always translate to effectiveness in real-world settings.

The use of the LA CAB/RPV as a complete regimen is generally not recommended in people with viremia due to suboptimal adherence to ART, or in people who have ongoing challenges with retention in HIV care. However, limited data from small observational studies found that LA CAB/RPV can lead to high levels of viral suppression in people who have struggled with adherence to oral ART and who are viremic at treatment initiation.[126-128] It should be noted that these studies were conducted in settings where LA CAB/RPV was available on Medicaid and ADAP formularies. Further, significant social and case management support, including full-time dedicated staff, was provided to ensure adherence to the regimen. This support was provided by multidisciplinary teams involving clinicians, pharmacists, and case managers and included appointment reminders, assistance with transportation, financial incentives, and assistance with rescheduling missed injection appointments. Additionally, injections were offered in people's homes, at harm-reduction sites, and via street medicine. It is unknown whether similar responses can be achieved in clinics without the resources to provide the level of adherence support seen in previous studies.

Based on these limited data, the Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to RPV or CAB, and with shared decision-making between providers and people with HIV **(CIII)**.

This approach may provide alternatives for individuals with viremia and difficulties with adherence to oral ART, especially for those at the highest risk for disease progression or death. If LA CAB/RPV is used, close monitoring is recommended, with drug-resistance testing performed if virologic response is inadequate. Importantly, conventional adherence support is likely inadequate, and expanded, intensive, multidisciplinary case management and outreach support are needed when using this strategy to assure adherence and adequate monitoring for people while on LA CAB/RPV. People with HIV and providers need to be aware of the significant risk of developing resistance to non-nucleoside reverse transcriptase inhibitors and particularly INSTIs if virologic failure occurs on LA CAB/RPV, which may limit future treatment options and may also lead to transmission of HIV; these concerns should be balanced with the given individual's HIV-related risk for disease progression and death. See Virologic Failure for a more detailed discussion.

Conclusion

Clinicians should obtain accurate information about a person's adherence and barriers to ART and appointment adherence, followed by meaningful discussions on solutions, rather than simply instructing adherence and warning about potential consequences of poor adherence. The latter approach fails to acknowledge a person's barriers to adherence, fails to provide actionable information, erodes rather than builds the patient–provider relationship, and has been demonstrated to not improve adherence.[129,130] At the same time, however, many of the interventions shown to improve adherence are difficult to implement in routine care. Nonetheless, effective lessons from this body of research can be applied to routine care to improve linkage to care, adherence to ART, and adherence to appointments. These lessons include the following:

- Regularly assess adherence to ART and appointments.
- Engage people struggling with adherence at any step on the care continuum with a constructive, collaborative, nonjudgmental, and problem-solving approach rather than reprimanding them or lecturing them on the importance of adherence.

- Elicit an individual's barriers to adherence, which may include personal, behavioral, medical, or structural barriers (e.g., substance use, housing instability, stigma, lack of transportation), clinic barriers (e.g., limited clinic hours, processes that make it more difficult to obtain prescriptions or schedule appointments), and system barriers (e.g., copays, prior approvals, processes that complicate maintaining pharmacy benefits or obtaining refills).
- Tailor approaches to improve adherence to an individual's specific needs and barriers, for example, by changing ART to simplify dosing or reduce side effects, finding resources to assist with copays or other out-of-pocket costs (see Table 19 below), to maintain an uninterrupted supply of ART, and to assure access to clinicians, or linking people to counseling to overcome stigma, substance use, or mental illness.
- Utilize ART regimens with high genetic barriers to resistance—such as DTG, bictegravir, or boosted darunavir regimens—for people with adherence problems. When selecting the regimen, consider possible side effects, out-of-pocket costs, convenience, and individual preferences, because the only regimen that will work is the one that people can obtain and are willing and able to take.
- Recognize the need for multidisciplinary approaches to identify and address barriers. Clinicians should help people with HIV understand the importance of adherence to the continuum of care, identify and address immediate barriers, and link them to resources for overcoming other obstacles.

Table 19. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy

Strategies	Examples
Provide an accessible, trustworthy, nonjudgmental multidisciplinary health care team.	• Include care providers, nurses, social workers, case managers, pharmacists, medication managers, and administrative staff on the care team; train all members on providing compassionate and person-centered care.
Strengthen early linkage to care and retention in care.	• Encourage health care team participation in linkage to and retention in care. • Use ARTAS training (if available). • Actively support linkage to care with assistance in making appointments and linkage to services to overcome barriers to care. • Streamline Ryan White HIV/AIDS Program eligibility verification processes for uninsured and underinsured clients.
Evaluate an individual's knowledge about HIV, HIV prevention, and HIV treatment and provide information based on this assessment.	• Keeping the current knowledge base in mind, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, therapeutic and prevention consequences of poor adherence, and the importance of staying in HIV care.
Identify facilitators, potential barriers to adherence, and necessary medication management skills both when starting ART and thereafter.	• Assess each individual's cognitive competence and impairment. • Assess behavioral and psychosocial challenges, including mental illnesses, trauma, social support levels, alcohol consumption, substance use, nondisclosure of HIV serostatus, and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of poor adherence). • Ask about medication-taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues, including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications, and transportation problems.
Provide needed resources.	• Provide or refer for mental health and/or substance use treatment. • Provide resources to obtain prescription drug coverage (e.g., AIDS Drug Assistance Programs, Pharmaceutical Company HIV Patient Assistance Programs and Cost-Sharing Assistance Programs). • Assist people during insurance enrollment periods to facilitate enrollment in plans that cover antiretrovirals. • Provide resources about stable housing, social support, transportation assistance, income, and food security.

Table 19. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy

Strategies	Examples
Involve people with HIV in ARV regimen selection.	• Review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of poor adherence. • Assess daily activities and tailor a regimen to predictable and routine daily events. • Consider preferential use of ART regimen with a high barrier to resistance, such as BIC-, DTG-, or boosted DRV-based ART if poor adherence is anticipated. • Consider the use of STR or fixed-dose-combination formulations to reduce pill burden and/or dosing frequency. • Consider the use of LA CAB/RPV if clinically appropriate (see the Long-Acting Antiretroviral Therapy section above for further discussion). • Assess if the cost or copayment for drugs will affect adherence and access to medications.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biological measure of adherence. • Use a simple behavioral rating scale or self-reported assessment. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white-coat adherence" responses. • Ensure that other members of the health care team also assess and support adherence.
Use positive reinforcement to foster adherence success.	• Inform people of the benefits of low or nondetectable levels of HIV viral load (e.g., "Undetectable = Untransmittable") and increases in CD4 counts. • Thank people for attending their appointments.
Identify the type of and reasons for poor adherence and target ways to improve adherence.	Identify if any of the following have contributed to poor adherence: • Failure to understand dosing instructions. • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements, polypharmacy). • Pill aversion or pill fatigue. • Adverse effects. • Inadequate understanding of drug resistance and its relationship to adherence. • Appointment reminders and incorporation of input from people with HIV in appointment scheduling. • Cost-related issues (e.g., copays for medications or visits, missed work time). • Mental illness, drug and alcohol use, homelessness, or poverty. • Stigma of taking pills or attending HIV-related appointments. • Nondisclosure of status or privacy concerns leading to missed doses, refills, or appointments.

Table 19. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy

Strategies	Examples
Select from among available effective adherence and retention interventions.	• See the CDC's Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention for a summary of best practice interventions to improve linkage, retention, and adherence. • Use adherence-related tools to complement education and counseling interventions (e.g., text messaging, pill box monitors, pill boxes, alarms). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates, transportation assistance, pharmacy delivery). • Use prescription assistance programs (see "Provide needed resources" above in this table). • Use motivational interviews. • Provide outreach for people who drop out of care. • Use peer or paraprofessional treatment navigators. • Recognize positive clinical outcomes resulting from better adherence. • Arrange for DOT for people in substance use treatment (if feasible). • Enhance clinic support and structures to promote linkage and retention (e.g., reminder calls, flexible scheduling, assessment of clinic service satisfaction). • Offer telehealth services for primary care, as well as supportive services when appropriate.
Systematically monitor retention in care.	• Record and follow up on missed visits.

Key: ART = antiretroviral therapy; ARTAS = Anti-Retroviral Treatment and Access to Services; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy; DRV = darunavir; DTG = dolutegravir; LA CAB/RPV = long-acting cabotegravir/rilpivirine; STR = single-tablet regimen

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Adverse Effects of Antiretroviral Agents

Updated: May 26, 2023
Reviewed: May 26, 2023

Adverse effects have been reported with all antiretroviral (ARV) drugs and were among the most common reasons for switching or discontinuing therapy, and for medication nonadherence in the earlier era of combination antiretroviral therapy (ART).[1] Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events. However, the long-term complications of ART can be underestimated because most clinical trials use highly specific inclusion criteria which exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short. As ART is recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy must be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects, including diabetes and other metabolic complications, atherosclerotic cardiovascular disease, kidney dysfunction, bone loss, and weight gain. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and managed. When selecting an ARV regimen, clinicians must consider potential adverse effects, as well as the individual's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications and include the following:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of adverse effects. For example, underlying liver disease from alcohol use, coinfection with viral hepatitis, and/or liver steatosis[2,3] may increase the risk of hepatotoxicity when efavirenz (EFV) or protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).
- Certain ARVs that may exacerbate pre-existing conditions. For example, psychiatric disorders may be exacerbated by EFV, rilpivirine, and, infrequently, by integrase strand transfer inhibitors.[4,5]
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications. For example, when pharmacokinetic boosters such as ritonavir or cobicistat are used, or when isoniazid is used with EFV.[6]
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,[7,8] EFV neuropsychiatric toxicity,[6,9] QTc prolongation,[10,11] and atazanavir (ATV)-associated hyperbilirubinemia.[12]

Information on the adverse effects of ARVs is outlined in several tables in these Guidelines. Table 20 provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 3, 4, 5, 6, 7, 8, 9, and 10.

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse effects for ARV drugs that are no longer commonly used in clinical practice (ddI, d4T, FPV/r, IDV, NFV, SQV/r, and TPV/r) have been removed from this table, with the exception of lipodystrophy and peripheral neuropathy associated with ddI and d4T. Because these effects may persist long after discontinuation of ddI or d4T, and patients may still present with these long-lasting toxicities, the drugs remain listed among the ARVs associated with these two effects. Refer to the product labels or to the archived July 10, 2019, version of the Guidelines for information regarding the adverse effects associated with these older ARVs.

This table focuses on ARV-associated adverse effects that a patient may experience as a result of taking an ARV regimen. For information regarding potential adverse effects of ARVs on fetuses and newborns when certain ARVs are taken around the time of conception or during pregnancy, refer to the Perinatal Guidelines.

In this table, N/A indicates either that there are no reported cases for that particular side effect or that data for that specific ARV drug class are not available. See Appendix B, Tables 3, 4, 5, 6, 7, 8, 9, and 10 for additional information listed by drug.

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Bone Density Effects	**TDF:** Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. **TAF:** Associated with smaller declines in BMD than those seen with TDF.	Decreases in BMD observed after the initiation of any ART regimen			N/A	Not evaluated
Bone Marrow Suppression	**ZDV:** Anemia, neutropenia.	N/A	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	**RPV and EFV:** QTc prolongation	**ATV/r and LPV/r:** PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	N/A	**FTR:** QTc prolongation was seen at four times the recommended dose. Use with caution in patients with pre-existing heart disease or QTc prolongation, or concomitant	N/A

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
					use of medications that may prolong QTc interval.	
Cardiovascular Disease	**ABC:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	**Boosted DRV and LPV/r:** Associated with cardiovascular events in some cohorts	N/A	N/A	N/A
Cholelithiasis	N/A	N/A	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A	N/A
Dyslipidemia	**ZDV > ABC:** ↑ TG and ↑ LDL **TAF:** ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	**EFV**: ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-boosted PIs:** ↑ TG, ↑ LDL, ↑ HDL **LPV/r > DRV/r and ATV/r:** ↑ TG	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	N/A	N/A
Gastrointestinal Effects	**ZDV > other NRTIs:** Nausea and vomiting	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) **LPV/r > DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	N/A	**LEN:** Nausea and diarrhea

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Hepatic Effects	**When TAF, TDF, 3TC, and FTC are withdrawn in patients with HBV/HIV coinfection or when HBV resistance develops:** Patients with HBV/HIV coinfection may develop severe hepatic flares. **ZDV:** Steatosis	**EFV:** Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported. **ATV:** Jaundice due to indirect hyperbilirubinemia	**DTG:** Persons with HBV or HCV coinfection may be at higher risk of DTG-associated hepatotoxicity.	**MVC:** Hepatotoxicity with or without rash or HSRs has been reported. **FTR:** Transaminase elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin observed in clinical trials.	N/A

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC: Contraindicated** if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks. **HSR symptoms (in order of descending frequency):** Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	**NVP:** Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	**RAL:** HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. **DTG:** Reported in <1% of patients in clinical development program	**MVC:** HSR reported as part of a syndrome related to hepatotoxicity.	N/A

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Injection Site Reaction		**RPV IM injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.		**CAB IM injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.	**T-20 SQ injection:** Reported in almost all patients; reactions may include pain, tenderness, nodules, induration, ecchymosis, erythema.	**LEN SQ injection:** Reported in 47–62% of patients; reactions may include swelling, erythema, pain, nodules, inflammation, induration. Nodules and induration may persist for months in some patients.
Lactic Acidosis	**Reported with older NRTIs, d4T, ZDV, and ddI,** but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A	N/A
Lipodystrophy	**Lipoatrophy:** Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, or TAF or TDF.	**Lipohypertrophy:** Trunk fat increase is observed with EFV-, PI-, and RAL-containing regimens; however, a causal relationship has not been established.			N/A	N/A
Myopathy/Elevated Creatine Phosphokinase	**ZDV:** Myopathy	N/A	N/A	**RAL and DTG:** ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A	N/A

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Nervous System/Psychiatric Effects	**History of exposure to ddI, ddC, or d4T:** Peripheral neuropathy (can be irreversible)	**Neuropsychiatric events:** EFV > RPV, DOR, ETR **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors. **RPV:** Depression, suicidality, sleep disturbances **DOR:** Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm	N/A	**All INSTIs:** Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A	**LEN:** Headache
Rash	**FTC:** Hyperpigmentation	All NNRTIs	ATV, DRV, and LPV/r	All INSTIs	MVC, IBA, FTR	N/A

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Therapy

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Renal Effects/ Urolithiasis	**TDF:** ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. **TAF:** Less impact on renal biomarkers and lower rates of proteinuria than TDF	**RPV:** Inhibits Cr secretion without reducing renal glomerular function	**ATV and LPV/r:** Associated with increased risk of chronic kidney disease in a large cohort study. **ATV:** Stone or crystal formation; adequate hydration may reduce risk **COBI (as a boosting agent for DRV or ATV):** Inhibits Cr secretion without reducing renal glomerular function	**DTG, COBI (as a boosting agent for EVG), and BIC:** Inhibits Cr secretion without reducing renal glomerular function	**IBA:** SCr abnormalities ≥Grade 3 reported in 10% of trial participants **FTR:** SCr >1.8 x ULN seen in 19% in a clinical trial, but primarily with underlying renal disease or other drugs known to affect creatinine	N/A
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV	Some reported cases for DRV, LPV/r, and ATV	RAL	N/A	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF and with DOR than with EFV.			INSTI > other ARV drug classes	N/A	N/A

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CI = capsid inhibitor; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQ = subcutaneous; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ULN = upper limit of normal; ZDV = zidovudine

Switching Antiretroviral Drugs Due to Adverse Effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life threatening (e.g., urolithiasis with ATV, renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient. When adverse effects occur during the use of a long-acting ARV, management might be challenging due to the persistence of drug in the body over the course of many months. Oral lead-in regimens for cabotegravir plus rilpivirine are available to assess short-term tolerability.

Switching a patient from an effective ARV agent or regimen to a new agent or regimen must be done carefully, and only when the potential benefits of the change outweigh the potential risks of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that drug-resistant viruses previously acquired or selected, even those not detected by past genotypic resistance testing, are archived in HIV reservoirs. The resistant virus, even if absent from subsequent resistance test results, may reappear under selective drug pressure. See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further discussion. It is critical that providers review the following information before implementing any treatment switch:

- The patient's medical and complete ARV history, including prior virologic responses to ART;
- All previous drug resistance test results;
- Viral tropism (if maraviroc [MVC] is being considered);
- HLA-B*5701 status (if ABC is being considered);
- Comorbidities;
- The patient's pregnancy status, ability to use effective contraceptives, and desire for pregnancy;
- Hepatitis B virus (HBV) status. Patients with evidence of chronic HBV infection should not discontinue ARVs active against HBV (e.g., TDF, tenofovir alafenamide, lamivudine, emtricitabine). If discontinuation is necessary due to adverse effects, consult the HBV/HIV Coinfection section for guidance;
- Adherence history;
- Prior intolerances to any ARVs; and
- Concomitant medications and supplements, considering any potential drug interactions with ARVs.

A patient's willingness to accept new food requirements or dosing schedule must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and

symptoms of comorbidities, adverse effects of concomitant medications, or HIV itself may mimic adverse effects caused by ART. Therefore, clinicians should investigate all potential causes for an adverse event. In the case of a severe adverse event, it may be necessary to discontinue or switch ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient's HIV viral load should also be monitored to assure continued viral suppression.

Table 21 lists several major ART-associated adverse events and the options for appropriate switches between agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in an effective ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment.

Table 21. Antiretroviral Therapy–Associated Adverse Effects That Can Be Managed With Substitution of Alternative Antiretroviral Agents

This table focuses on ARV-associated adverse effects that patients may experience as a result of a current ARV regimen. For information regarding ARV choices to use in individuals of childbearing potential and during pregnancy to avoid potential ARV adverse effects on fetuses and newborns refer to the Perinatal Guidelines.

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	TAF or ABC[b] NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered, if appropriate.	Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.
Bone Marrow Suppression	ZDV	Regimen not including ZDV	ZDV has been associated with neutropenia and macrocytic anemia.
Calculi Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	This switch should be made if ATV is the presumed cause of the calculi.
Cardiac QTc Interval Prolongation	EFV, RPV, FTR	Boosted ATV or DRV, DOR, or INSTI-based regimen (that does not combine with RPV)	High EFV, RPV, and FTR exposures may cause QT prolongation. Consider switching from EFV- or RPV- based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes. For FTR, if there is no alternative ARV drug option, consider switching the concomitant medication.
Cardiovascular Events Myocardial infarction, ischemic stroke	ABC	TDF or TAF	ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.
	RTV- or COBI-boosted PI regimens, EFV	INSTI, RPV, or DOR	If lipids are a concern, see Dyslipidemia below. Large observation cohorts have found an association between some PIs (DRV, FPV, IDV, LPV/r) and an increased risk of CV events. However, this association has not been seen with ATV. Further study is needed.

Table 21. Antiretroviral Therapy–Associated Adverse Effects That Can Be Managed With Substitution of Alternative Antiretroviral Agents

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted PI, EFV-based regimens	INSTI, DOR, or RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	Boosted ATV or DRV, INSTI, NNRTI	GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient and do not warrant ARV substitution unless they are persistent and intolerable.
	Other RTV- or COBI-boosted regimens	BIC, DTG, RAL, or NNRTI	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC.
Hypersensitivity Reaction	ABC	Any appropriate ABC-sparing regimen	Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.
	EFV, ETR, NVP, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 counts.
	DTG, RAL	Non-INSTI ART	Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases.
	MVC	Suitable alternative ART	
Insulin Resistance	LPV/r	INSTI, NNRTI	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r on insulin resistance. However, traditional risk factors for insulin resistance may be stronger risk factors than the use of any PI.
Jaundice and Icterus	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.
Lipoatrophy	Peripheral lipoatrophy (loss of subcutaneous fat of the limbs, face, and buttocks) is associated with prior thymidine analog (d4T and ZDV) use. Despite switching from these ARVs, fat recovery remains slow (may take years) and incomplete.		
Lipohypertrophy	Accumulation of visceral, truncal, dorsocervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse lipohypertrophy.		
Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression, ataxia, encephalopathy	EFV, RPV	DOR, ETR, PI/c, or PI/r INSTIs may be used, but monitoring is recommended (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug, but in some patients, ataxia or encephalopathy may appear months to years after EFV-initiation. Persistent or intolerable effects should prompt substitution of EFV. INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.

Table 21. Antiretroviral Therapy–Associated Adverse Effects That Can Be Managed With Substitution of Alternative Antiretroviral Agents

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen	Mild rashes that develop after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.
	DRV/c, DRV/r	ATV/c, ATV/r, or another drug class (e.g., INSTI)	Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.
Renal Effects Including proximal renal tubulopathy and elevated creatinine	TDF[a]	ABC,[b] TAF (for patients with CrCl >30 mL/min, unless on chronic hemodialysis), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate.	TDF may cause tubulopathy. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting.
	ATV/c, ATV/r, LPV/r	BIC, DTG, EVG/c/TAF/FTC, RAL, boosted DRV, or NNRTI	COBI, DTG, BIC, and, to a lesser extent, RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient for renal dysfunction if SCr increases by >0.4 mg/dL.

[a] In patients with chronic active HBV infection, another agent that is active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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Cost Considerations and Antiretroviral Therapy

Updated: September 12, 2024
Reviewed: September 12, 2024

The clinical benefits, public health impact, and cost-effectiveness of HIV treatment have been well-established since the advent of combination antiretroviral therapy (ART),[1-6] and the expanded use of ART is one of the four pillars of the *Ending the HIV Epidemic in the U.S.* initiative.[7,8] However, HIV treatment with ART is costly. A 2015 study using 2012 health care expenditure data estimated that the discounted lifetime medical costs for an individual who acquires HIV at 35 years of age are $326,500 ($597,300 undiscounted), with 60% of the costs attributable to ART.[9] The estimated total direct expenditure for HIV care and treatment between 2002 and 2011 was $10.7 billion annually, which is 800% to 900% higher than similar expenditures for other chronic conditions.[10] Since the addition of the cost table in these guidelines in 2012,[11] the overall cost of brand-name, first-line antiretroviral (ARV) regimens increased by over 30% from 2012 to 2018,[12] which is 3.5 times higher than the rate of inflation for the same period. Total annual undiscounted spending on ARV drugs has more than doubled since 2010, reaching $22.5 billion in 2018.[13,14]

This section provides guidance on cost considerations related to HIV clinical care. The cost of ART, especially out-of-pocket costs to the person with HIV, should be one of the many considerations in regimen selection, because such expenditures may directly affect adherence. Overall costs to the health care system, to insurers, and to society are also important, especially given the increasing number of people with HIV, rising drug costs, and increasing multimorbidity among people aging with HIV. Providers should make every effort to prevent costs from limiting HIV care.

Cost Sharing in the United States

Prescription drug pricing in the United States involves complex systems with varying requirements for mandatory and voluntary discounts, rebates, and reimbursement rates, and much of the pricing information is confidential. Prices can vary depending on the state, purchaser, type of public or private insurance coverage in use, and number of generic competitors to branded drugs (see Table 22b below). Additionally, provider-administered drugs and biologics, including those used in the management of HIV (e.g., intramuscular injections of long-acting cabotegravir plus rilpivirine [LA CAB/RPV]), are typically associated with product, administration, and/or office visit costs. Therefore, providers may find it difficult to navigate payer cost-containment practices, including formulary restrictions; prior authorization requirements; and cost-sharing arrangements, such as copayments (a fixed dollar amount per prescription), coinsurance (a fixed percentage of the prescription cost), and insurance deductible payments.

Out-of-pocket costs for people with HIV can be prohibitive, creating a barrier to the initiation and continuation of ART. Cost sharing results in higher rates of people not initiating ART, prescription abandonment at the pharmacy, decreased adherence, and more frequent drug discontinuation. In turn, these may lead to worse health outcomes and an increased use of the medical system, especially among people with chronic diseases.[15-20] Conversely, reducing out-of-pocket costs (e.g., through manufacturer copayment-assistance programs or by prescribing generic drugs instead of more costly brand-name products) has been associated with improved adherence.[21] Given the clear association between out-of-pocket costs and the ability to pay for and adhere to medications, clinicians should minimize out-of-pocket drug-related expenses for people with HIV whenever possible. However,

many of the cost-sharing arrangements that determine out-of-pocket costs are not transparent to clinicians or people with HIV at the time decisions on ART are made.

Maximum allowable copayments on prescription drugs covered by Medicaid can vary by family income, but they are usually nominal. For commercial insurers, cost sharing is generally subject to maximum payment rules under the Affordable Care Act (ACA). Manufacturer cost-sharing assistance programs are available for most brand-name ARV products but may be restricted by pharmacy and by state. Manufacturer copay assistance may also be subject to copay accumulator programs implemented by insurers' pharmacy benefit managers, whereby manufacturer payments do not count toward a person's deductible or out-of-pocket maximum.

Medicare Part D plan cost sharing can include deductibles and copayments or coinsurance, including out-of-pocket payments of up to 25% on prescription drugs, until total out-of-pocket spending reaches approximately $3,300 in 2024 and $2,000 in 2025.[22-25] Medicare Part B cost sharing on provider-administered drugs, such as LA CAB/RPV or ibalizumab-uiyk (IBA) infusions, can be up to 20% of all medication costs.[26] Low-income beneficiaries may qualify for subsidies to defray Part D cost-sharing payments or for the Qualified Medicare Beneficiary program to defray Part B cost-sharing payments. Beginning in 2025, Medicare Advantage and Part D plans will be required to offer beneficiaries an option to enroll in a Medicare Prescription Payment Plan authorized under the Inflation Reduction Act of 2022, allowing beneficiaries to pay out-of-pocket prescription drug costs in the form of capped monthly payments instead of a single payment in full at the pharmacy.[27] Manufacturer copay assistance programs may not be applied toward Medicare plan cost sharing, but assistance from independent foundations (e.g., Patient Access Network Foundation, Patient Advocate Foundation) may provide cost-sharing support if financial eligibility criteria are met.

AIDS Drug Assistance Programs (ADAPs), through the Ryan White HIV/AIDS Program (RWHAP), make ARVs and other prescription drugs accessible to people with HIV who are underinsured and have limited financial resources. Furthermore, many ADAPs provide premium and cost-sharing assistance to eligible clients covered by Medicaid, commercial insurance plans, or Medicare.[28]

Generic Antiretrovirals and Multi-Tablet Regimens

The U.S. health care system saved $408 billion in 2022 from using generic drugs and biosimilar products, including $130 billion in Medicare savings and $194 billion in savings for commercial insurers.[29]

With substantial improvements in the long-term safety and effectiveness of contemporary ART, a number of regimens and regimen components in Tables 6a and 6b remain listed beyond their patent protection date and are or will be available as lower-cost generic options. In one study, the savings associated with a transition to a hypothetical lower-cost generic ART could potentially help cover the 20-year, $480 billion projected costs to reach national treatment targets.[5]

Some research informs the cost impact of using specific generic ARV regimens or regimen components. In a cost-effectiveness analysis conducted before the availability of integrase strand transfer inhibitors (INSTIs), the use of generic efavirenz (EFV) had an estimated savings of nearly $1 billion, and a regimen with generic EFV was very cost-effective.[2] Another study described a 25% reduction in both the wholesale acquisition cost (WAC)and federal supply schedule cost associated with switching from branded coformulated dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) to branded DTG plus generic ABC and generic 3TC.[2,30]

A number of generic options for ARV regimen components included in Tables 6a and 6b are commercially available. See Table 22b below for a summary of the costs associated with commonly used generic and proprietary ARV regimen components and coformulations.

There is keen interest in assessing the economic value of using newer, more expensive drugs compared with older, less expensive drugs that have established clinical safety and efficacy. One study investigated the cost-effectiveness of TDF-based versus tenofovir alafenamide (TAF)–based regimens.[22] The study demonstrated that the similar efficacy—but slightly improved toxicity profile—of the TAF-based regimens would justify a $1,000 higher annual premium for the TAF-based regimens. The study further highlighted that once generic TDF becomes available at much lower costs, TAF-based regimens will remain cost-effective only if their annual cost is no more than $1,000 above that of generically available TDF-based regimens. Of note, generic TDF was approved in 2018.

The use of DTG plus generic 3TC for initial therapy has been evaluated in a cost-containment analysis. One study projected that if just 50% of people with newly diagnosed HIV initiated a two-pill regimen consisting of branded DTG plus generic 3TC, the cost savings would reach $550 million to $800 million over 5 years.[31] If 25% of people with sustained viral suppression switched to branded DTG plus generic 3TC maintenance therapy, cost savings were projected to exceed $3 billion in just 5 years.[31]

Because all commercially available STRs are branded products, including those containing ARV components that are no longer patent protected, use of generics in the United States may necessitate modest increases in pill burden, but without changes in drug frequency. One study of Medicare Part D spending, which included expenditures for one ARV fixed-dose combination tablet (ABC/3TC), demonstrated that separating brand-name coformulated products into their generic components could have saved Medicare an estimated $2.7 billion from 2011 through 2016, and it highlighted this approach as a critical cost-containment measure.[32] A benefit of STRs is that they eliminate the risk that one drug in the regimen will be temporarily or permanently discontinued because of prescribing error, unsynchronized refill schedules, or prohibitive out-of-pocket costs. Data to support or refute the superiority of once-daily STRs versus once-daily multi-tablet regimens, particularly based on virologic outcomes and especially following viral suppression, remain limited. One large observational cohort study demonstrated a small but statistically significant virologic efficacy benefit associated with STRs.[33] In this study, the time to treatment discontinuation was shorter for non-STRs than for STR once-daily regimens; however, this difference disappeared when modifications for regimen simplification were included in the analysis. On the other hand, observational data from Spain showed that coformulated DTG/ABC/3TC resulted in similar viral suppression compared to DTG plus ABC/3TC, both when used as an initial ARV regimen and when persons with viral suppression on STR were switched to the two-pill formulation as a cost-saving strategy.[34]

Importantly, when the costs of brand-name drug products and generic ARV drugs are compared, savings associated with generic ARV drugs may vary when branded drugs are subject to discounts or rebates across public and private payer systems. Although generic drug products may be associated with societal cost savings and, specifically, savings for public payers, commercial insurers, and people with HIV with significant out-of-pocket pharmacy expenses, manufacturer copay assistance is not generally available to commercially insured individuals. In cases where manufacturer copay assistance may be available for a brand-name ARV product but not for the equivalent generic product, the generic drug prescription may paradoxically result in higher out-of-pocket costs.

Costs and Cost-Effectiveness of ARV Regimens for Highly Treatment-Experienced People With Multidrug-Resistant HIV

For people with multidrug-resistant (MDR) HIV, an ARV regimen that includes intravenous IBA, subcutaneous lenacapavir, or oral fostemsavir can be effective in achieving viral suppression, but with high associated costs. Two cost-effectiveness analyses using independent simulation models have demonstrated that IBA-containing ARV regimens would substantially improve survival for people with MDR HIV but at a high cost per quality-adjusted life-year, given the high cost of IBA. However, the overall budget impact of such regimens would be relatively small, given the limited number of people for whom IBA would be necessary.[35,36]

Laboratory Services

In the context of lifelong ART, the amount of money saved by performing infrequent or one-time tests (e.g., genotypes, serologies) is modest, even for expensive tests. Even so, judicious use of laboratory testing, without compromising individual care, can still be an important way to reduce costs. For people with deductibles for laboratory tests, decreasing the use of tests with limited clinical value could reduce costs and improve adherence to a care plan. Several studies have examined the value of laboratory services in HIV care. One cost analysis study suggested that there may be no clinical benefit to continuing CD4 T lymphocyte (CD4) cell monitoring in people with suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[19] In the United States, reducing biannual CD4 monitoring to annual monitoring could save approximately $10 million per year.[37] Another study reviewed the records of 429 hospitalizations for 274 people with HIV at a single site during a 6-month period. The inpatient chart review demonstrated that 45% of ordered laboratory tests were not indicated, including hepatitis serologies, other serologies, and cytomegalovirus polymerase chain reaction tests. During this 6-month period, the estimated cost of excess and inappropriate laboratory testing totaled between $14,000 and $92,000.[38]

Cost-effectiveness analyses from 2001 and 2005 demonstrated the value of genotypic resistance testing in people who are ART-experienced and ART-naive and supported the recommendation by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) to perform resistance testing before ART initiation and at time of virologic failure.[39,40] More recent cost-effectiveness analyses have revisited the value of baseline, pre-treatment genotype testing in the setting of INSTI plus two-nucleoside reverse transcriptase inhibitor (NRTI) regimens. One modeling study suggested that INSTI-specific genotype testing before initiation of a regimen including DTG plus two NRTIs was not cost-effective and may lead to underutilization of INSTIs; the results highlighted that some people with minor INSTI resistance mutations would still become virologically suppressed on a DTG-based regimen.[41] A second modeling study found that standard (NRTI, non-nucleoside reverse transcriptase inhibitor, protease inhibitor) genotype testing before ART initiation was also not cost-effective, because it may have little impact on outcomes given the use of regimens including an INSTI plus two NRTIs in first-line treatment.[42] Both of these modeling studies assessed the use of genotype testing only for decision-making for initial ART and presumed that such testing would be available for use at the time of first-line failure. The results of these modeling studies suggest that additional clinical research is needed to define the role of genotypic resistance testing before initiation of a regimen including an INSTI plus two NRTIs. Importantly, these modeling data do not apply to the initiation of two-drug ARV regimens (e.g., DTG plus 3TC) or to people who have received cabotegravir (CAB) as pre-exposure prophylaxis (PrEP), which are both being prescribed increasingly in clinical practice. It should be noted that the Panel continues to recommend baseline

testing for clinically relevant protease and reverse transcriptase mutations for most people, with additional genotypic resistance testing for integrase mutations for individuals with a history of CAB use for PrEP (see Drug-Resistance Testing).

Costs and Cost-Effectiveness of Comprehensive HIV Care

Comprehensive person-centered HIV care offers substantial clinical benefits.[43] Such programs include integration of social service needs and services for mental health, substance use disorders, sexual health, and age-associated multimorbidity (see Substance Use Disorders and HIV, Transgender People With HIV, Adherence to the Continuum of Care, and HIV and the Older Person). Integrated services can improve engagement in care and virologic suppression among people with HIV, but they require investment and resources. Several cost-effectiveness analyses have demonstrated that integrated care programs can offer excellent value, especially if delivered to people at increased risk of disengagement in care.[44-46]

Health care access in the United States can be inequitable and limited, depending on location and income. Although the ACA has substantially improved access to HIV clinical services in many regions of the United States since 2010, an estimated 36% of people with HIV in the United States live in the 11 states that had not expanded Medicaid in accordance with the ACA as of August 2020.[28]

The RWHAP provides a critical source of outpatient HIV clinical care for people with HIV who have low income and remain uninsured or underinsured under the ACA, or who require wraparound support.[28] A recent cost-effectiveness analysis underscored the value of this safety net program and projected its clinical and cost impact over 50 years. Given higher rates of virologic suppression among people with HIV attending RWHAP clinics (compared with estimated virologic suppression in the absence of such supports), the analysis projects fewer HIV incident infections and longer life expectancy and demonstrates the cost-effectiveness of RWHAP.[47] However, because RWHAP is focused on HIV care and support services, people with HIV who have other important outpatient and inpatient health needs may experience underdiagnosis and undertreatment if they cannot pay the out-of-pocket costs of clinical care.

Comprehensive HIV care and treatment often require navigating a complex, dynamic patchwork of service delivery, and both payer and financing mechanisms. Provider awareness of this patchwork, including the array of services available to people with HIV eligible for RWHAP, is therefore essential to maximizing clinical outcomes.

Conclusion

Ideally, costs should not drive clinical care, yet they are a factor in contemporary health care. Because regimen costs may affect the ability of people with HIV to afford and adhere to therapy, understanding ART-related costs in the United States is increasingly important. Providers play a key role in ensuring optimal care while working to both (1) minimize costs for ARV drugs and avoid or minimize unnecessary laboratory monitoring and (2) retain excellent clinical outcomes in an environment of cost-containment strategies, including formulary restrictions, utilization management (e.g., prior authorization), and cost-sharing. Therefore, providers should remain informed of current insurance and payment structures, ART costs (see Table 22b below for estimates of average drug prices), out-of-pocket expenditure requirements, and available generic ARV options. Providers should work with people with HIV and their pharmacists, social workers, case managers, and peer

navigators to understand the medication benefits and any potential financial barriers to prescription fulfillment and full adherence for each person with HIV. This information will help providers identify treatment options that are safe, effective, and affordable. Engaging people with HIV in discussion about cost constraints during regimen selection will likely facilitate adherence. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company assistance programs for people who qualify) and refer them to such assistance if needed. Similarly, providers should help people with HIV to find comprehensive clinical care coverage when available and consider opportunities to integrate care when feasible.

Table 22a. Insurance and Health Program Prescription Drug Pricing and Access

Insurance/Health Program	Prescription Drug Pricing and Access
Medicaid	Drug manufacturers must participate in the MDRP for their drugs to be covered by Medicaid and under Medicare Part B. Manufacturers are required to pay Medicaid programs a rebate of at least 23.1% of the AMP for most brand-name drugs (13% for generics) sold to retail pharmacies or outpatient care providers (notably infused, injected, implanted, inhaled, or instilled drugs). Manufacturers pay additional rebates if this confidential AMP increases faster than the CPI-U rate of inflation. Additionally, many states negotiate with manufacturers for supplemental rebates. States are permitted to require "nominal" cost sharing for medical and pharmacy benefits for some beneficiaries, although many elect not to do so. States can obtain a waiver to allow them to apply higher cost sharing.
Medicare	ARVs are one of six "protected drug classes" under Medicare Part D. Part D plans must provide access to all, or substantially all, FDA-approved ARVs. Part D plan sponsors, or PBMs on their behalf, negotiate rebates on outpatient drugs with manufacturers; the extent of rebating is unclear. Most physician-administered drugs and biologics are covered under Medicare Part B at a set cost: ASP plus 6%. This pricing mechanism controls spending by narrowing the spread between what is actually paid for the drug and what is actually billed to Medicare. Premiums and cost-sharing payments may be significant for both services and prescription drugs, although caps on out-of-pocket spending for drugs covered under Medicare Part D went into effect in 2024; Part A (hospital care) and Part B place no cap on out-of-pocket spending. Some subsidies and supplemental coverage are offered for low-income beneficiaries. Manufacturer copay assistance programs cannot be applied to Part B or Part D cost sharing; cost-sharing support is available from ADAPs, foundations, and other sources and is based on financial eligibility criteria.
Commercial Insurance	Private insurance plans, or PBMs on their behalf, negotiate rebates on inpatient and outpatient drugs with manufacturers; the extent of rebating is unclear. Formulary restrictions and utilization management (prior authorization, step therapy, higher cost sharing) involving drugs and biologics covered under plans' pharmacy benefit or medical benefit (e.g., infused or injected ARVs) are possible cost-containment measures. Cost sharing can be highly variable. Manufacturer copay assistance programs can be applied in most cases but may not count toward annual ACA cost-sharing limits; cost-sharing support is also available from ADAPs, foundations, and other sources and is based on financial eligibility criteria.

Table 22a. Insurance and Health Program Prescription Drug Pricing and Access

Insurance/Health Program	Prescription Drug Pricing and Access
ADAPs	Significant discounting on most ARVs negotiated by the ADAP Crisis Task Force is allowed under the 340B Drug Pricing Program. There is usually no cost sharing for ADAP clients who are uninsured. ADAP can assist with commercial or public insurance out-of-pocket costs.
Veterans Affairs	The FCP is the maximum price manufacturers may charge the four largest federal purchasers of pharmaceuticals (the "Big Four"): the U.S. Department of Veterans Affairs (VA), Department of Defense, Public Health Service (including the Indian Health Service), and the Coast Guard. The FCP of a drug includes a 24% discount on a drug's average price paid by non-federal purchasers. Additional discounts may be applied if non-federal purchase prices increase faster than the CPI-U inflation rate. Big Four prices may be 40% to 50% below list prices. The VA may negotiate further price reductions. Prescription drug cost sharing is generally nominal; medications are not withheld from those who cannot afford cost-sharing expenses.
Community Health Centers	Many community health centers are enrolled in the 340B Drug Pricing Program, which allows discounted drug purchasing using the MDRP formula. Discounts start at 23.1% off AMP, with additional discounts if the AMP increases faster than the CPI-U rate of inflation. Cost sharing in community health centers is first driven by payer source. For clients who are uninsured, cost sharing, if required, is typically based on a sliding fee scale.

Key: ACA = Affordable Care Act; ADAP = AIDS Drug Assistance Program; AMP = average manufacturer price; ARV = antiretroviral; ASP = average sales price; CPI-U = consumer price index-urban; FCP = federal ceiling price; FDA = U.S. Food and Drug Administration; MDRP = Medicaid Drug Rebate Program; PBM = pharmacy benefits manager

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

Table 22b includes three benchmark prices, rounded to the nearest dollar, for commonly used antiretroviral (ARV) drugs[a] as a general reference for health care providers when considering the cost of HIV treatment. Health care providers should contact pharmacies or payers regarding actual prices, comparative cost savings, formulary restrictions, and cost-sharing requirements. The wholesale acquisition cost (WAC) is the list price published by manufacturers for prescription drugs or biologics sold to wholesalers. The WAC price approximates what retail pharmacies pay wholesalers for single-source (e.g., brand-name) drugs. There is a range of WAC prices for generic ARV drugs because these are multiple-source products with variable list prices. With increasing competition, actual transactional prices of generic drugs decrease substantially among wholesalers and pharmacies. Average wholesale price (AWP) has historically been used as the basis for setting public (e.g., Medicaid) and private (e.g., commercial insurer) reimbursement rates for pharmacies. Neither WAC nor AWP includes variable price concessions along supply and payment chains, including discounts and rebates to wholesalers, pharmacies, federal purchasers (e.g., the Department of Veterans Affairs), pharmacy benefit managers, commercial insurers, Medicaid, 340B pharmacies, and AIDS Drug Assistance Programs. The availability of these discounts and rebates depends on product demand, market competition, and WAC price increases set by manufacturers. Maximum Medicaid payment rates are assigned to generic products with three or more therapeutically and pharmaceutically equivalent products, as determined by the U.S. Food and Drug Administration. This federally established pharmacy reimbursement limit is the federal upper limit (FUL). Federal Medicaid will reimburse state Medicaid programs up to this limit for multiple-source drugs (plus the dispensing fee); states may set their own state maximum allowable costs and commercial insurers set their own reimbursement upper limits with pharmacies. While WACs and AWPs are generally set annually, FULs are adjusted on a monthly basis, particularly for multiple-source drugs with fluctuating pharmacy acquisition costs. In this table, the FUL for a drug is described as "pending" if a generic drug currently lacks the required competition.

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
NRTIs					
Abacavir					
Generic	300-mg tablet	60 tablets	$100 to $150	$578 to $603	$48
Ziagen	300-mg tablet	60 tablets	$559	$670	N/A
Emtricitabine					
Generic	200-mg capsule	30 capsules	$390 to $464	$482 to $579	Pending

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
Emtriva	200-mg capsule	30 capsules	$537	$644	N/A
Lamivudine					
Generic	300-mg tablet	30 tablets	$40 to $415	$429	$39
Epivir	300-mg tablet	30 tablets	$416	$499	N/A
Tenofovir Disoproxil Fumarate					
Generic	300-mg tablet	30 tablets	$27 to $300	$167 to $1,216	$42
Viread	300-mg tablet	30 tablets	$1,254	$1,504	N/A
Zidovudine					
Generic	300-mg tablet	60 tablets	$36 to $54	$54 to $365	$13
NRTI Combination Products					
Abacavir/Lamivudine					
Generic	600-mg/300-mg tablet	30 tablets	$100 to $302	$1,393 to $1,395	$40
Tenofovir Alafenamide/Emtricitabine					
Descovy	25-mg/200-mg tablet	30 tablets	$2,202	$2,643	N/A
Tenofovir Disoproxil Fumarate/Emtricitabine					
Generic	300-mg/200-mg tablet	30 tablets	$25 to $420	$70 to $2,100	$15
Truvada	300-mg/200-mg tablet	30 tablets	$1,842	$2,211	N/A
Tenofovir Disoproxil Fumarate/Lamivudine					
Cimduo	300-mg/300-mg tablet	30 tablets	$1,185	$1,422	N/A
Zidovudine/Lamivudine					
Generic	300-mg/150-mg tablet	60 tablets	$125 to $578	$265 to $932	$44

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
NNRTIs					
Efavirenz					
Generic	600-mg tablet	30 tablets	$80 to $894	$1,043 to $1,118	$55
Doravirine					
Pifeltro	100-mg tablet	30 tablets	$1,760	$2,112	N/A
Etravirine					
Generic	200-mg tablet	60 tablets	$1,287	$1,609	$878
Intelence	200-mg tablet	60 tablets	$1,469	$1,762	N/A
Nevirapine					
Generic	200-mg tablet	60 tablets	$10 to $45	$648 to $651	$47
Generic XR	400-mg tablet	30 tablets	$135 to $565	$595 to $706	$149
Viramune XR	400-mg tablet	30 tablets	$840	$1,008	N/A
Rilpivirine					
Edurant	25-mg tablet	30 tablets	$1,483	$1,780	N/A
PIs					
Atazanavir					
Generic	200-mg capsule	60 capsules	$178 to $316	$1,502 to $1,668	$711
Reyataz	200-mg capsule	60 capsules	$1,463	$1,756	N/A
Generic	300-mg capsule	30 capsules	$178 to $316	$1,502 to $1,652	$187
Reyataz	300-mg capsule	30 capsules	$1,449	$1,739	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
Atazanavir/Cobicistat					
Evotaz	300-mg/150-mg tablet	30 tablets	$1,605	$1,927	N/A
Darunavir					
Generic	600-mg tablet	60 tablets	$60 to $1,145	$1,373 to $2,388	Pending
Prezista	600-mg tablet	60 tablets	$2,158	$2,590	N/A
Generic	800-mg tablet	30 tablets	$60 to $1,153	$1,384 to $2,388	Pending
Prezista	800-mg tablet	30 tablets	$2,158	$2,590	N/A
Prezista	100-mg/mL suspension	200 mL	$1,199	$1,439	N/A
Darunavir/Cobicistat					
Prezcobix	800-mg/150-mg tablet	30 tablets	$2,467	$2,960	N/A
Lopinavir/Ritonavir					
Generic	200-mg/50-mg tablet	120 tablets	$885	$1,106	Pending
Kaletra	200-mg/50-mg tablet	120 tablets	$1,024	$1,229	N/A
Tipranavir					
Aptivus	250-mg capsule	120 capsules	$2,054	$2,466	N/A
INSTIs					
Dolutegravir					
Tivicay	50-mg tablet	30 tablets	$2,257	$2,709	N/A
Tivicay	50-mg tablet	60 tablets	$4,514	$5,418	N/A
Raltegravir					
Isentress	400-mg tablet	60 tablets	$1,997	$2,396	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
Isentress HD	600-mg tablet	60 tablets	$1,997	$2,396	N/A
Fusion Inhibitor					
Enfuvirtide					
Fuzeon	90-mg injection kit	60 doses (1 kit)	$3,586	$4,303	N/A
CCR5 Antagonist					
Maraviroc					
Generic	150-mg tablet	60 tablets	$1,141	$1,764	$1,659
Selzentry	150-mg tablet	60 tablets	$1,730	$2,076	N/A
Generic	300-mg tablet	60 tablets	$1,141	$1,764	$1,518
Selzentry	300-mg tablet	60 tablets	$1,730	$2,076	N/A
Selzentry	300-mg tablet	120 tablets	$3,460	$4,152	N/A
CD4-Directed Post-Attachment Inhibitor					
Ibalizumab-uiyk					
Trogarzo	200-mg vial	8 vials	$11,840	$14,208	N/A
gp120-Directed Attachment Inhibitor					
Fostemsavir					
Rukobia	600-mg tablet	60 tablets	$9,010	$10,812	N/A
Capsid Inhibitor					
Lenacapavir					
Sunlenca	300-mg tablet	4 tablets	$3,250	$3,900	N/A
Sunlenca	300-mg tablet	5 tablets	$4,063	$4,875	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
Sunlenca	927-mg injection kit	2 vials (1 kit every 6 months)	$19,500 (every 6 months)	$23,400 (every 6 months)	N/A
Coformulated Combination Products as Single-Tablet Regimens					
Bictegravir/Tenofovir Alafenamide/Emtricitabine					
Biktarvy	50-mg/25-mg/200-mg tablet	30 tablets	$3,981	$4,777	N/A
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
Symtuza	800-mg/150-mg/10-mg/ 200-mg tablet	30 tablets	$4,717	$5,660	N/A
Dolutegravir/Abacavir/Lamivudine					
Triumeq	50-mg/600-mg/300-mg tablet	30 tablets	$3,748	$4,497	N/A
Dolutegravir/Lamivudine					
Dovato	50-mg/300-mg tablet	30 tablets	$2,977	$3,572	N/A
Dolutegravir/Rilpivirine					
Juluca	50-mg/25-mg tablet	30 tablets	$3,512	$4,215	N/A
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine					
Delstrigo	100-mg/300-mg/300-mg tablet	30 tablets	$2,680	$3,216	N/A
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine					
Generic	600-mg/300-mg/200-mg tablet	30 tablets	$82 to $252	$302 to $3,414	$54
Atripla	600-mg/300-mg/200-mg tablet	30 tablets	$2,995	$3,594	N/A
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine					
Symfi	600-mg/300-mg/150-mg tablet	30 tablets	$1,926	$2,312	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
Symfi Lo	400-mg/300-mg/150-mg tablet	30 tablets	$1,926	$2,312	N/A
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
Genvoya	150-mg/150-mg/10-mg/ 200-mg tablet	30 tablets	$33,981	$4,777	N/A
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine					
Stribild	150-mg/150-mg/300-mg/ 200-mg tablet	30 tablets	$4,176	$5,012	N/A
Rilpivirine/Tenofovir Alafenamide/Emtricitabine					
Odefsey	25-mg/25-mg/200-mg tablet	30 tablets	$3,623	$4,348	N/A
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine					
Complera	25-mg/300-mg/200-mg tablet	30 tablets	$3,454	$4,145	N/A
Copackaged Combination Products as Injectable Regimens					
Cabotegravir + Rilpivirine					
Cabenuva	600 mg (3 mL) 900 mg (3 mL)	2 vials (every other month)	$6,624 (every other month)	$7,948 (every other month)	N/A
Cabenuva	400 mg (2 mL) 600 mg (2 mL)	2 vials	$4,416	$5,299	N/A
PK Enhancers (Boosters)					
Cobicistat					
Tybost	150-mg tablet	30 tablets	$297	$357	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

ARV Drug (Generic and Brand Names)	Strength, Formulation	Capsules, mLs, Tablets, or Vials	Wholesale Acquisition Cost[b]	Average Wholesale Price[b]	Federal Upper Limit (As of July 31, 2024)[c]
		(Monthly Values, Unless Otherwise Noted)			
Ritonavir					
Generic	100-mg tablet	30 tablets	$80 to $160	$278	$74
Norvir	100-mg tablet	30 tablets	$257	$309	N/A

[a] The following less commonly used ARV drugs are not included in this table: fosamprenavir and nelfinavir.

[b] **Source:** Micromedex Red Book [database]. Merative. 2024. Available at: https://www.micromedexsolutions.com.

[c] **Source:** Federal Upper Limits–March 2024 [database]. Medicare & Medicaid Services. 2024. Available at: https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; HD = high dose; INSTI = integrase strand transfer inhibitor; N/A = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; XR = extended release

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Drug–Drug Interactions

Updated: September 12, 2024
Reviewed: September 12, 2024

Overview

Pharmacokinetic (PK) drug–drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. In some instances, changes in drug exposure may increase the frequency and/or severity of toxicities or affect therapeutic responses. When prescribing or switching one or more drugs in an ARV regimen, clinicians must consider the potential for drug–drug interactions—both those affecting ARVs and those affecting concomitant drugs. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a specific drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways and drug transporter systems are prescribed concomitantly. When it is necessary to prescribe interacting drugs, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities. Tables 24a through 25b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modification of ARVs or concomitant medicines or for alternative therapy.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common drug interaction mechanisms are described and listed for individual ARV drugs in Table 23 below.

Pharmacokinetic Interactions Affecting Drug Absorption

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acid-reducing agents—such as proton pump inhibitors, H2 antagonists, or antacids—can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir and rilpivirine).
- Products that contain polyvalent cations—such as supplements, iron products, or antacids that contain aluminum, calcium, or magnesium—can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme cytochrome P450 (CYP) 3A4 or efflux transporter P-glycoprotein in the intestines may reduce or promote the absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are most frequently responsible for clinically significant drug interactions:

- The CYP enzyme system is responsible for the metabolism of many drugs, including non-nucleoside reverse transcriptase inhibitors, protease inhibitors, the CCR5 antagonist maraviroc, and the INSTI elvitegravir. CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARV drugs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
- The uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTIs cabotegravir and raltegravir. Drugs that induce or inhibit the UGT enzyme can affect the PK of these INSTIs.
- The INSTIs bictegravir and dolutegravir (DTG) and the capsid inhibitor lenacapavir have mixed metabolic pathways, including both CYP3A4 and UGT1A1. Drugs that induce or inhibit these enzymes may have variable impact on the PK of these ARVs.

Pharmacokinetic Enhancers (Boosters)

PK enhancing is a strategy used to increase exposure of an ARV by concomitantly administering a drug that inhibits the enzymes that metabolize the ARV. Currently, two agents are used as PK enhancers: ritonavir (RTV) and cobicistat (COBI). Both drugs are potent inhibitors of the CYP3A4 enzyme and, thus, when coadministered with ARVs metabolized by the CYP3A4 pathway, the resultant systemic exposure of the ARVs is higher. Importantly, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. Complex or unknown mechanisms of PK-based interactions preclude extrapolation of RTV drug interactions to certain COBI interactions, such as interactions with warfarin, direct oral anticoagulants, phenytoin, voriconazole, oral contraceptives, and certain hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

Drug transporters are expressed in various tissues, and they play an important role in drug disposition. Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic cation transporters in renal tubular cells. Similar transporters aid hepatic, renal, and biliary clearance of drugs and may be susceptible to drug interactions. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these drug transporters. The influence of drug transporters on drug–drug interactions is complex, and the clinical significance of these interactions is unclear but is under investigation. Further research is needed to better understand these pathways and the clinical significance of this drug interaction mechanism.

Role of Therapeutic Drug Monitoring in Managing Drug–Drug Interactions

Therapeutic drug monitoring (TDM) can guide the dosing of certain medications by using measured drug concentrations to improve the likelihood of desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The “therapeutic range” is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

When concomitant use of an ARV drug and another medication is likely to result in a clinically important drug–drug interaction, the first step is to assess whether other, equally effective treatment options can be

used to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Drug concentration assays for some ARV drugs are commercially available; however, result reporting may take 1 week or longer. When interpreting assay results, clinicians should consider the patient's medication adherence, the timing of the patient's last ARV dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If needed, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take. If a dose adjustment is needed, TDM must be repeated after the dose-adjusted drug reaches steady state to ensure appropriate dosing.

TDM information should not be used alone; it must be considered in conjunction with other clinical information—including virologic response, medication adherence, and signs and symptoms of drug toxicities—to assure safe and effective therapy.

Table 23. Mechanisms of Antiretroviral-Associated Drug Interactions

Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the antiretroviral (ARV) drug and/or the interacting drug. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and cytochrome P450 (CYP)– and uridine diphosphate glucuronosyltransferase (UGT) 1A1–mediated interactions.

Note: N/A indicates that there are no clinically relevant interactions by the mechanism. Identified mechanisms are specific to the ARV drugs described in the row and may not be reflective of complete ARV regimens. Some older ARVs—unboosted atazanavir, fosamprenavir, nelfinavir, nevirapine, tipranavir, and zidovudine—are not commonly used in clinical practice and are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions for these ARVs.

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
INSTIs							
BIC	N/A	Concentrations of PO INSTIs are decreased by-products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn).	Substrate	3A4	N/A	N/A	Substrate
CAB	N/A		Substrate	N/A	N/A	N/A	Substrate
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate
EVG/c	N/A		Inhibitor	3A4	3A4, 2D6	2C9	Substrate
RAL	N/A		N/A	N/A	N/A	N/A	Substrate
PIs							
ATV/c	Concentration decreased	N/A	Substrate, inhibitor	3A4	3A4, 2D6, 2C8	N/A	Inhibitor
ATV/r	Concentration decreased	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6, 2C8	1A2, 2B6, 2C8, 2C9, 2C19	**ATV:** Inhibitor **RTV:** Inducer
DRV/c	N/A	N/A	Substrate, inhibitor	3A4	3A4, 2D6	N/A	No data
DRV/r	N/A	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
LPV/r	N/A	N/A	Substrate	3A4, 2D6	3A4	1A2, 2B6, 2C8, 2C9, 2C19	Inducer

Table 23. Mechanisms of Antiretroviral-Associated Drug Interactions

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
NNRTIs							
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A
RPV	**Only RPV PO:** Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A
NRTIs							
ABC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
Capsid Inhibitor							
LEN (SQ and PO)	N/A	N/A	Substrate	3A4	3A4	N/A	Substrate
CCR5 Antagonist							
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
gp120-Directed Attachment Inhibitor							
FTR	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
Fusion Inhibitor							
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 23. Mechanisms of Antiretroviral-Associated Drug Interactions

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; Ca = calcium; CAB = cabotegravir; CCR5 = C-C chemokine receptor type 5; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; FTR = fostemsavir; gp120 = glycoprotein 120; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; P-gp = P-glycoprotein; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase; Zn = zinc

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Updated: September 12, 2024
Reviewed: September 12, 2024

This table provides information on the known or predicted interactions between protease inhibitors (PIs) and non-antiretroviral (ARV) drugs. The term "PI" refers to atazanavir (ATV) or darunavir (DRV) boosted with either ritonavir (RTV or r) or cobicistat (COBI or c). This table does not include interactions for unboosted ATV, fosamprenavir (FPV), lopinavir (LPV), nelfinavir (NFV), or tipranavir (TPV). For information regarding interactions between PIs and other ARV drugs, including dosing recommendations, refer to Tables 24c, 25a, and 25b.

Recommendations for managing a particular drug interactions may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication.

Note: Unboosted ATV, FPV, LPV/r, NFV, and TPV are no longer commonly used in clinical practice in the United States and are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions between these PIs and concomitant medications. Information regarding these agents may also be found in archived versions of this guideline.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV/c, ATV/r	**When Given Simultaneously** • ↓ ATV expected	Administer ATV at least 2 hours before or 2 hours after antacids or buffered medications.
H2 Receptor Antagonists	ATV/c, ATV/r	↓ ATV expected	H2RA dose should not exceed a dose equivalent to famotidine 40 mg twice daily in ART-naive patients or famotidine 20 mg twice daily in ART-experienced patients. Give ATV 300 mg (plus COBI 150 mg **or** RTV 100 mg) with food simultaneously with and/or ≥10 hours after the dose of H2RA.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
			If using TDF and H2RA in ART-experienced patients, administer ATV 400 mg plus RTV 100 mg with food simultaneously with and/or ≥10 hours after the dose of H2RA. **Do not coadminister** ATV/c with TDF and H2RA in ART-experienced patients.
	DRV/c, DRV/r	**With Ranitidine** • ↔ DRV/r	No dose adjustment needed
Proton Pump Inhibitors	ATV/c, ATV/r	**With Omeprazole 40 mg** • ATV AUC ↓ 76% **When Omeprazole 20 mg Is Given 12 Hours Before ATV/c or ATV/r** • ATV AUC ↓ 42%	PPI dose should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r. **Do not coadminister** in PI-experienced patients.
	DRV/c	↔ PI expected	No dose adjustment needed
	DRV/r	↔ DRV/r Omeprazole AUC ↓ 42%	Consider alternative ARV or acid reducer. If coadministered, monitor for omeprazole effectiveness. If the patient does not experience symptomatic relief, increase the dose to no more than omeprazole 40 mg daily.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	ATV/c, ATV/r, DRV/c, DRV/r	↑ alfuzosin expected	**Contraindicated**
Doxazosin	ATV/c, ATV/r, DRV/c, DRV/r	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate. Monitor blood pressure. Dose reduction may be necessary.
Tamsulosin	ATV/c, ATV/r, DRV/c, DRV/r	↑ tamsulosin expected	**Do not coadminister** unless benefits outweigh risks. If coadministered, monitor blood pressure.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Terazosin	ATV/c, ATV/r, DRV/c, DRV/r	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate. Monitor blood pressure. Dose reduction may be necessary.
Silodosin	ATV/c, ATV/r, DRV/c, DRV/r	↑ silodosin expected	**Contraindicated**
Antibacterials—Antimycobacterials			
Bedaquiline	ATV/c, ATV/r, DRV/c, DRV/r	• ↑ bedaquiline possible	**Do not coadminister** unless benefits outweigh risks. If coadministered, consider therapeutic drug monitoring and monitor for bedaquiline-related adverse effects, including hepatotoxicity and QTc prolongation.
Rifabutin	ATV/r	**Compared With Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) Plus ATV/r** • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	Recommended dose is rifabutin 150 mg once daily. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. Monitor for rifabutin-related adverse events, including neutropenia and uveitis. PK data in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants.
	DRV/r	**Compared With Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) Plus DRV/r** • ↔ rifabutin AUC and metabolite AUC ↑ 881%	
	ATV/c, DRV/c	↑ rifabutin expected ↓ COBI expected	**Do not coadminister.**
Rifampin	ATV/c, ATV/r, DRV/c, DRV/r	↓ PI concentration by >75%	**Contraindicated.** Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. Increasing the COBI dose **is not recommended.** Consider rifabutin if a rifamycin is indicated.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifapentine	ATV/c, ATV/r, DRV/c, DRV/r	**Daily and Weekly Dosing** • ↓ PI expected	**Do not coadminister.**
Antibacterials—Macrolides			
Azithromycin	ATV/c, ATV/r	↑ azithromycin possible	No dose adjustment needed
	DRV/c, DRV/r	↔ azithromycin expected	No dose adjustment needed
Clarithromycin	ATV/c, ATV/r, DRV/c	↑ clarithromycin expected ↑ ATV/r and PI/c expected	Consider alternative ARV or azithromycin.
	DRV/r	DRV/r ↑ clarithromycin AUC 57% RTV 500 mg twice daily ↑ clarithromycin 77%	Consider alternative ARV or azithromycin. If use of clarithromycin is necessary in a patient with impaired renal function, reduce clarithromycin dose by 50% in patients with CrCl 30 to 60 mL/min. In patients with CrCl <30 mL/min, reduce clarithromycin dose by 75%. Monitor for clarithromycin-related adverse events, including QTc prolongation.
Erythromycin	ATV/c, ATV/r, DRV/c, DRV/r	↑ erythromycin expected ↑ PI expected	Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	ATV/c, ATV/r, DRV/c, DRV/r	↑ apixaban expected	**Do not coadminister** in patients who require apixaban 2.5 mg twice daily. **In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily** • Reduce apixaban dose by 50%.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Dabigatran	ATV/c, ATV/r	**With COBI 150 mg Alone** • Dabigatran AUC ↑ 110% to 127% **With ATV/r** • ↑ dabigatran expected	**Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation in Adult Patients** • CrCl >30 mL/min: no dose adjustment needed • CrCl ≤30 mL/min: do not coadminister. **Treatment and Reduction in the Risk of Recurrence of DVT and PE or Prophylaxis of DVT and PE Following Hip Replacement Surgery in Adult Patients** • CrCl ≥50 mL/min: no dose adjustment needed • CrCl <50 mL/min: do not coadminister.
	DRV/c, DRV/r	**With DRV/c** • Single dose DRV/c: dabigatran AUC ↑ 164% • After 14 days of DRV/c: dabigatran AUC ↑ 88% **With DRV/r** • Single dose DRV/r: dabigatran AUC ↑ 72% • After 14 days of daily DRV/r: dabigatran AUC ↑ 18%	
Edoxaban	ATV/c, ATV/r, DRV/c	↑ edoxaban expected	**Treatment of Nonvalvular Atrial Fibrillation** • No dose adjustment needed **Treatment of DVT and PE** • Reduce edoxaban dose to 30 mg once daily.
	DRV/r	↑ edoxaban expected	**Treatment of Nonvalvular Atrial Fibrillation** • No dose adjustment needed **Treatment of DVT and PE** • No dose adjustment needed
Rivaroxaban	ATV/c, ATV/r, DRV/c, DRV/r	↑ rivaroxaban expected	**Do not coadminister.**

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Warfarin	ATV/c, DRV/c	↑ warfarin possible	Monitor INR closely when stopping or starting PI/c or PI/r and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.
	ATV/r, DRV/r	↓ warfarin possible	
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below			
Antidepressants, Anxiolytics			
Bupropion	ATV/r, DRV/r	↓ bupropion possible	Titrate bupropion dose based on clinical response.
	ATV/c, DRV/c	↔ bupropion expected	No dose adjustment needed
Buspirone	ATV/c, ATV/r, DRV/c, DRV/r	↑ buspirone expected	Administer lowest dose of buspirone with caution and titrate buspirone dose based on clinical response. Dose reduction may be necessary. Monitor for buspirone-related adverse events.
Desvenlafaxine	ATV/c, ATV/r, DRV/c, DRV/r	↑ desvenlafaxine possible	No dose adjustment needed
Duloxetine	ATV/c, DRV/c	↑ duloxetine possible	No dose adjustment needed
	ATV/r, DRV/r	↑ or ↓ duloxetine possible	
Mirtazapine	ATV/c, ATV/r, DRV/c, DRV/r	↑ mirtazapine possible	Monitor for mirtazapine-related adverse events. Mirtazapine dose reduction may be necessary.
Nefazodone	ATV/c, ATV/r, DRV/c, DRV/r	↑ nefazodone expected ↑ PI possible	Monitor for nefazodone-related adverse events and PI tolerability.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Selective Serotonin Reuptake Inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine)	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response.
	ATV/c, ATV/r, DRV/c	↑ or ↓ SSRI possible	Titrate SSRI dose using the lowest available initial or maintenance dose.
Trazodone	ATV/c, ATV/r, DRV/c, DRV/r	**RTV 200 mg Twice Daily (For 2 Days)** • Trazodone ↑ AUC 240%	Administer lowest dose of trazodone and titrate dose based on clinical response. Monitor for trazodone-related adverse events, including CNS and CV adverse events.
Tricyclic Antidepressants (e.g., amitriptyline, doxepin, nortriptyline)	ATV/c, ATV/r, DRV/c, DRV/r	↑ TCA expected	Administer lowest possible TCA dose and titrate based on clinical assessment and/or drug concentrations. Monitor for TCA-related adverse events.
Venlafaxine	ATV/c, ATV/r, DRV/c, DRV/r	↑ venlafaxine and O-desmethylvenlafaxine expected	Monitor for venlafaxine-related adverse events. Consider venlafaxine dose reduction.
Antipsychotics			
Aripiprazole	ATV/c, ATV/r, DRV/c, DRV/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for effectiveness/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6-poor metabolizers.
Brexpiprazole	ATV/c, ATV/r, DRV/c, DRV/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate the dose based on clinical monitoring for effectiveness/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6-poor metabolizers.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cariprazine	ATV/c, ATV/r, DRV/c, DRV/r	↑ cariprazine expected	**Starting Cariprazine in a Patient Who Is Already Receiving a PI** • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased. **Starting a PI in a Patient Who Is Already Receiving Cariprazine** • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce the dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, the cariprazine dose may need to be increased.
Iloperidone	ATV/c, ATV/r, DRV/c, DRV/r	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lumateperone	ATV/c, ATV/r, DRV/c, DRV/r	↑ lumateperone expected	**Do not coadminister.**
Lurasidone	ATV/c, ATV/r, DRV/c, DRV/r	↑ lurasidone expected	**Contraindicated**
Olanzapine, Olanzapine/Samidorphan	ATV/c, DRV/c	↔ olanzapine expected ↑ samidorphan possible	No dose adjustment needed
	ATV/r, DRV/r	↓ olanzapine possible	Monitor for therapeutic effectiveness of olanzapine.
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., clozapine, perphenazine, risperidone, thioridazine)	ATV/c, ATV/r, DRV/c, DRV/r	↑ antipsychotic possible	Titrate the antipsychotic dose using the lowest initial dose or adjust the maintenance dose accordingly. Monitor for adverse events, including QTc prolongation.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Pimavanserin	ATV/c, ATV/r, DRV/c, DRV/r	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg once daily.
Pimozide	ATV/c, ATV/r, DRV/c, DRV/r	↑ pimozide expected	**Contraindicated**
Quetiapine	ATV/c, ATV/r, DRV/c, DRV/r	↑ quetiapine expected	**Starting Quetiapine in a Patient Receiving a PI** • Initiate quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse events, including QTc prolongation. **Starting a PI in a Patient Receiving a Stable Dose of Quetiapine** • Consider alternative ARV. If coadministered, reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine effectiveness and adverse events, including QTc prolongation.
Ziprasidone	ATV/c, ATV/r, DRV/c, DRV/r	↑ ziprasidone expected	Monitor for ziprasidone-related adverse events, including QTc prolongation.
Antimigraine			
Ergot Derivatives	ATV/c, ATV/r, DRV/c, DRV/r	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated**
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists			
Atogepant	ATV/c, ATV/r, DRV/c, DRV/r	↑ atogepant expected	Chronic migraine: **Do not coadminister.** Episodic migraine: Administer atogepant at a dose of 10 mg once daily.
Rimegepant	ATV/c, ATV/r, DRV/c, DRV/r	↑ rimegepant expected	**Do not coadminister.**
Ubrogepant	ATV/c, ATV/r, DRV/c, DRV/r	↑ ubrogepant expected	**Contraindicated**

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Zavegepant	ATV/r, ATV/c, DRV/c	↑ zavegepant expected	**Do not coadminister.**
	DRV/r	↔ zavegepant expected	No dose adjustment needed
Serotonin 5-HT1B, 1D Receptor Agonists			
Almotriptan	ATV/c, ATV/r, DRV/c, DRV/r	↑ almotriptan expected	Administer single dose of almotriptan 6.25 mg. Maximum dose should not exceed 12.5 mg in a 24-hour period.
Eletriptan	ATV/c, ATV/r, DRV/c, DRV/r	↑ eletriptan expected	**Contraindicated**
Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan Zolmitriptan	ATV/c, ATV/r, DRV/c, DRV/r	↔ triptan expected	No dose adjustment needed
Antifungals			
Fluconazole	ATV/c, ATV/r, DRV/c, DRV/r	↔ PI expected ↔ fluconazole expected	No dose adjustment needed
Isavuconazole	ATV/c, DRV/c	↑ isavuconazole expected ↓ PI possible	**Contraindicated**
	ATV/r, DRV/r	↑ isavuconazole expected ↓ PI possible	If coadministered, monitor isavuconazole concentrations and monitor for isavuconazole-related adverse events. Monitor for PI tolerability.
Ibrexafungerp	ATV/c, ATV/r, DRV/c, DRV/r	↑ ibrexafungerp expected	Reduce ibrexafungerp dose to 150 mg twice daily.
Itraconazole	ATV/c, ATV/r, DRV/c, DRV/r	↑ itraconazole expected ↑ PI expected	Itraconazole doses >200 mg/day **are not recommended** unless dosing is guided by itraconazole concentrations.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Posaconazole	ATV/r	ATV AUC ↑ 146% ↔ posaconazole possible	If coadministered, monitor for PI-related adverse events.
	ATV/c, DRV/c, DRV/r	↑ PI expected ↔ posaconazole possible	
Voriconazole	ATV/c, DRV/c	No data	**Do not coadminister** voriconazole and RTV or COBI unless benefits outweigh risks. If coadministered, monitor voriconazole concentration and adjust dose accordingly.
	ATV/r, DRV/r	RTV 100 mg twice daily ↓ voriconazole AUC 39%	
Antimalarials			
Artemether/Lumefantrine	ATV/c, DRV/c	↑ lumefantrine expected ↑ artemether possible	Clinical significance is unknown. If coadministered, monitor closely for antimalarial effectiveness and lumefantrine-related adverse events, including QTc prolongation.
	DRV/r	↔ artemether expected ↔ DHA[a] expected Lumefantrine AUC ↑ 175% ↔ DRV	
Artesunate	ATV/c	↑ DHA[a] possible	Monitor for artesunate-related adverse effects.
	DRV/c	↔ DHA[a] expected	No dose adjustment needed
	ATV/r, DRV/r	↓ DHA[a] possible	Monitor for clinical response to artesunate.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Atovaquone/Proguanil	ATV/r, DRV/r	**With ATV/r** • Atovaquone AUC ↓ 46% • Proguanil AUC ↓ 41% **With DRV/r** • ↓ atovaquone/proguanil possible	Clinical significance is unknown. Consider alternative ARV or malaria prophylaxis.
	ATV/c, DRV/c	↔ atovaquone/proguanil expected	No dose adjustment needed
Mefloquine	ATV/c, ATV/r, DRV/c, DRV/r	**With RTV 200 mg Twice Daily** • RTV AUC ↓ 31% and C_{min} ↓ 43% • ↔ mefloquine **With ATV (Unboosted), PI/c, or PI/r** • ↑ mefloquine possible	Clinical significance is unknown. Consider alternative ARV or antimalarial drug. If coadministered, monitor for mefloquine-related adverse events, including psychiatric symptoms and QTc prolongation. Monitor virologic response.
Antiplatelets			
Clopidogrel	ATV/c, ATV/r, DRV/c, DRV/r	Clopidogrel active metabolite AUC ↓ 69% in people with HIV on RTV or COBI-boosted regimens compared with healthy volunteers without HIV. Impaired platelet inhibition observed in people with HIV.	**Do not coadminister.**
Prasugrel	ATV/c, ATV/r, DRV/c, DRV/r	Prasugrel active metabolite AUC ↓ 52% in people with HIV on RTV or COBI-boosted regimens compared to healthy volunteers without HIV. Adequate platelet inhibition observed in people with HIV.	No dose adjustment needed
Ticagrelor	ATV/c, ATV/r, DRV/c, DRV/r	↑ ticagrelor expected	**Do not coadminister.**

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Vorapaxar	ATV/c, ATV/r, DRV/c, DRV/r	↑ vorapaxar expected	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis			
Atovaquone Oral suspension	ATV/r	↔ atovaquone	No dose adjustment needed
	ATV/c, DRV/c, DRV/r	↔ atovaquone expected	No dose adjustment needed
Antiseizure			
Carbamazepine	ATV/r	↑ carbamazepine possible May ↓ PI concentrations substantially	Consider alternative ARV or anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assess virologic response. Carbamazepine dose reduction may be necessary.
	DRV/r	Carbamazepine AUC ↑ 45% ↔ DRV	Monitor anticonvulsant concentration and adjust dose accordingly.
	ATV/c, DRV/c	↑ carbamazepine possible ↓ COBI expected ↓ PI expected	**Contraindicated**
Eslicarbazepine	ATV/c, ATV/r, DRV/c, DRV/r	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Ethosuximide	ATV/c, ATV/r, DRV/c, DRV/r	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; monitor lamotrigine concentration or consider alternative ARV or anticonvulsant.
	DRV/r	↓ lamotrigine possible	

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ATV/c	No data	Monitor anticonvulsant concentration and adjust dose accordingly.
	DRV/c	↔ lamotrigine expected	No dose adjustment needed.
Oxcarbazepine	ATV/c, ATV/r, DRV/c, DRV/r	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Phenobarbital	ATV/r, DRV/r	↓ phenobarbital possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	ATV/c, DRV/c	↓ COBI expected ↓ PI expected	**Contraindicated**
Phenytoin	ATV/r, DRV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	ATV/c, DRV/c	↓ COBI expected ↓ PI expected	**Contraindicated**
Primidone	ATV/c, ATV/r, DRV/c, DRV/r	↓ PI expected	**Do not coadminister.**
Valproic Acid	ATV/c, ATV/r, DRV/c, DRV/r	↓ or ↔ VPA possible	Monitor VPA concentrations and monitor for PI tolerability.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antivirals—Hepatitis C			
Elbasvir/Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold Elbasvir ↔ ATV Grazoprevir ↑ ATV AUC 43%	**Contraindicated** May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
	DRV/r	Elbasvir AUC ↑ 66% Grazoprevir AUC ↑ 7.5-fold ↔ DRV	
	ATV/c, DRV/c	↑ grazoprevir expected	
Glecaprevir/Pibrentasvir	ATV/c, ATV/r	**With (ATV 300 mg Plus RTV 100 mg) Once Daily** • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	**Contraindicated**
	DRV/c, DRV/r	**With (DRV 800 mg Plus RTV 100 mg) Once Daily** • Glecaprevir AUC ↑ fivefold • ↔ pibrentasvir	**Do not coadminister.**

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Ledipasvir/Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose adjustment needed Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased risk of TDF toxicities. If coadministration is necessary, monitor for TDF-related adverse events.
	ATV/c, DRV/c, DRV/r	↔ PI expected ↔ ledipasvir and sofosbuvir	
Sofosbuvir/Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment needed
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓ 28% ↔ velpatasvir	No dose adjustment needed
	ATV/c, DRV/c	↔ sofosbuvir and velpatasvir expected	No dose adjustment needed
Sofosbuvir/Velpatasvir/ Voxilaprevir	ATV/c, ATV/r	**With ATV/r** • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	**Do not coadminister.**
	DRV/c, DRV/r	**With DRV/r** • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antivirals—Miscellaneous (e.g., for CMV, Mpox)			
Brincidofovir	ATV/c, ATV/r, DRV/c, DRV/r	↑ brincidofovir possible	Give PI dose at least 3 hours after administering brincidofovir and monitor for brincidofovir-related adverse events (i.e., elevations in ALT/AST and bilirubin and GI adverse events).
Cidofovir	ATV/c, ATV/r, DRV/c, DRV/r	↔ cidofovir	No dose adjustment needed
Tecovirimat	ATV/c, ATV/r, DRV/c, DRV/r	↔ tecovirimat	No dose adjustment needed
Antivirals—SARS-CoV-2			
Molnupiravir	ATV/c, ATV/r, DRV/c, DRV/r	↔ molnupiravir	No dose adjustment needed
Remdesivir	ATV/c, ATV/r, DRV/c, DRV/r	↔ remdesivir	No dose adjustment needed
Ritonavir-Boosted Nirmatrelvir	ATV/r, ATV/c, DRV/c, DRV/r	↑ PI expected ↑ ritonavir-boosted nirmatrelvir expected	No dose adjustment needed. Monitor for increased ritonavir-boosted nirmatrelvir and PI-related adverse events.
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	ATV/c, ATV/r	↑ arformoterol possible	No dose adjustment needed
	DRV/c, DRV/r	↔ arformoterol expected	No dose adjustment needed
Indacaterol	ATV/c, ATV/r, DRV/c, DRV/r	**With RTV 300 mg Twice Daily** • Indacaterol AUC ↑ 1.7-fold	No dose adjustment needed in patients receiving indacaterol 75 mcg daily.
Olodaterol	ATV/c, ATV/r, DRV/c, DRV/r	↑ olodaterol expected	No dose adjustment needed
Salmeterol	ATV/c, ATV/r, DRV/c, DRV/r	↑ salmeterol possible	**Do not coadminister,** due to potential increased risk of salmeterol-related CV events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Antiarrhythmics			
Amiodarone	ATV/r	↑ amiodarone possible ↑ PI possible	**Contraindicated**
	ATV/c, DRV/c, DRV/r	↑ amiodarone possible ↑ PI possible	**Do not coadminister** unless the benefits outweigh the risks. If coadministered, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone drug concentration.
Digoxin	ATV/c, ATV/r, DRV/c, DRV/r	RTV 200 mg twice daily ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41% and ↔ AUC	Monitor digoxin concentrations. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Disopyramide	ATV/c, ATV/r, DRV/c, DRV/r	↑ disopyramide possible	**Do not coadminister.**
Dofetilide	ATV/c, ATV/r, DRV/c, DRV/r	↑ dofetilide possible	**Do not coadminister.**
Dronedarone	ATV/c, ATV/r, DRV/c, DRV/r	↑ dronedarone expected	**Contraindicated**
Flecainide	ATV/c, ATV/r, DRV/c, DRV/r	↑ flecainide possible	Consider alternative ARV or antiarrhythmic. If coadministered, monitor flecainide concentrations and for antiarrhythmic-related adverse events.
Lidocaine	ATV/c, ATV/r, DRV/c, DRV/r	↑ lidocaine possible	Consider alternative ARV or antiarrhythmic. If coadministered, monitor lidocaine concentrations and for antiarrhythmic-related adverse events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Mexiletine	ATV/c, ATV/r, DRV/c, DRV/r	↑ mexiletine possible	Consider alternative ARV or antiarrhythmic. If coadministered, monitor mexiletine concentrations and for antiarrhythmic-related adverse events.
Propafenone	ATV/c, ATV/r, DRV/c, DRV/r	↑ propafenone possible	**Do not coadminister.**
Quinidine	ATV/r	↑ quinidine expected	**Contraindicated**
	ATV/c, DRV/c, DRV/r	↑ quinidine possible	**Do not coadminister.**
Sotalol	ATV/c, ATV/r, DRV/c, DRV/r	↔ sotalol expected	No dose adjustment needed
Beta-Blockers			
Atenolol, Labetalol	ATV/c, ATV/r, DRV/c, DRV/r	↑ beta-blockers possible	No dose adjustment needed
Bisoprolol, Carvedilol, Metoprolol, Nebivolol	ATV/c, ATV/r, DRV/c, DRV/r	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP2D6 enzymes (e.g., atenolol, labetalol, nadolol).
Calcium Channel Blockers			
Amlodipine, Diltiazem, Felodipine, Nifedipine, Verapamil	ATV/c, ATV/r, DRV/c, DRV/r	↑ dihydropyridine possible ↑ verapamil possible	Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.
Diltiazem	ATV/c, ATV/r	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ of diltiazem AUC is likely with ATV/c or ATV/r	Decrease diltiazem dose by at least 50%. If starting diltiazem, start with the lowest dose and titrate according to clinical response and adverse events. ECG monitoring is recommended.
	DRV/c, DRV/r	↑ diltiazem possible	Titrate diltiazem dose according to clinical response and adverse events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac—Other			
Bosentan	ATV/c, ATV/r, DRV/c, DRV/r	**With ATV (Unboosted)** • ↓ ATV expected **With PI/r or PI/c** • ↑ bosentan expected	**Do not coadminister** bosentan and unboosted ATV. **In Patients on a PI (Other Than Unboosted ATV) >10 Days** • Start bosentan at 62.5 mg once daily or every other day. **In Patients on Bosentan Who Require a PI (Other Than Unboosted ATV)** • Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day. **When Switching Between COBI and RTV** • Maintain same bosentan dose.
Eplerenone	ATV/c, ATV/r, DRV/c, DRV/r	↑ eplerenone expected	**Contraindicated**
Ivabradine	ATV/c, ATV/r, DRV/c, DRV/r	↑ ivabradine expected	**Contraindicated**
Mavacamten	ATV/c, ATV/r, DRV/c, DRV/r	↑ mavacamten expected	**Contraindicated**
Ranolazine	ATV/c, ATV/r, DRV/c, DRV/r	↑ ranolazine expected	**Contraindicated**
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg twice daily ↑ 17-BMP AUC 2-fold	No dose adjustment needed
	ATV/c, ATV/r, DRV/c	↔ 17-BMP expected	No dose adjustment needed

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	ATV/c, ATV/r, DRV/c, DRV/r	↑ glucocorticoids possible RTV 100 mg twice daily ↑ fluticasone AUC 350-fold	**Do not coadminister** unless the potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse events associated with corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider alternative inhaled/intranasal corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	ATV/c, ATV/r, DRV/c, DRV/r	↑ glucocorticoids possible ↓ PI possible	**Do not coadminister** unless the potential benefits of systemic corticosteroid outweigh the risks of adverse events associated with systemic corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	ATV/c, ATV/r, DRV/c, DRV/r	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	ATV/c, ATV/r, DRV/c, DRV/r	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of adverse events associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events.
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	ATV/c, ATV/r, DRV/c, DRV/r	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Glucose-Lowering			
Canagliflozin	ATV/c, DRV/c	↔ canagliflozin	No dose adjustment needed
	ATV/r, DRV/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, increase canagliflozin dose to 200 mg daily. If a patient is already tolerating canagliflozin 200 mg daily and requires additional glycemic control, management strategy is based on renal function. **In Patients With eGFR ≥60 mL/min/1.73 m²** • Canagliflozin dose may be increased to 300 mg daily. **In Patients With eGFR <60 mL/min/1.73 m²** • Consider adding another antihyperglycemic agent.
Saxagliptin	ATV/c, ATV/r, DRV/c, DRV/r	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/Saxagliptin	ATV/c, ATV/r, DRV/c, DRV/r	↑ saxagliptin expected	**Do not coadminister.** Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended.**
Herbal Products			
St. John's Wort	ATV/c, ATV/r, DRV/c, DRV/r	↓ PI expected	**Contraindicated**
Hormonal Therapies—Contraceptives			
Injectable Contraceptives Depot MPA	ATV/c, ATV/r, DRV/c, DRV/r	↔ expected	No dose adjustment needed

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Oral Contraceptives (e.g., desogestrel, drospirenone, ethinyl estradiol, levonorgestrel, norgestimate, norethindrone)	ATV/c	Drospirenone AUC ↑ 130% Ethinyl estradiol AUC ↓ 22%	**Contraindicated** with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia**.** Use alternative ARV or alternative contraceptive methods.
		↔ ethinyl estradiol AUC and C_{min} ↓ 25% ↔ levonorgestrel	No dose adjustment needed
	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate AUC ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[c]
		↑ drospirenone expected ↔ estetrol	Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods.
	DRV/c	Drospirenone AUC ↑ 58% Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods.
	DRV/r	Ethinyl estradiol AUC ↓ 44% and C_{min} ↓ 62% Norethindrone AUC ↓ 14% and C_{min} ↓ 30%	**When Used for Contraception** • Consider alternative ARV or contraceptive methods. If combined, consider using an oral contraceptive with at least 35 mcg of ethinyl estradiol. **When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation)** • Monitor for clinical effectiveness of hormonal therapy.
Subdermal Implant Contraceptives (e.g., etonogestrel, levonorgestrel)	ATV/c, ATV/r, DRV/c, DRV/r	↑ etonogestrel, levonorgestrel expected	No dose adjustment needed

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Transdermal Contraceptives (e.g., ethinyl estradiol/norelgestromin, ethinyl estradiol/levonorgestrel)	ATV/c, ATV/r, DRV/c, DRV/r	↓ ethinyl estradiol possible with ritonavir ↑ ethinyl estradiol possible with cobicistat ↑ norelgestromin, levonorgestrel possible	No dose adjustment needed
Vaginal Ring Contraceptives (e.g., etonogestrel/ethinyl estradiol, segesterone/ethinyl estradiol)	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	No dose adjustment needed with etonogestrel/ethinyl estradiol vaginal rings. Use alternative ARV or contraceptive methods with segesterone/ethinyl estradiol vaginal rings.
	ATV/c, DRV/c, DRV/r	↓ ethinyl estradiol possible with ritonavir ↑ ethinyl estradiol possible with cobicistat	
Emergency Contraceptives Levonorgestrel (oral)	ATV/c, ATV/r, DRV/c, DRV/r	↑ levonorgestrel expected	No dose adjustment needed
Hormonal Therapies—Gender Affirming and Menopause			
Estradiol	ATV/c, DRV/c	↓ or ↑ estradiol possible	Adjust estradiol dose as needed based on clinical effects and endogenous hormone concentrations.
	ATV/r, DRV/r	↓ estradiol possible	
5-Alpha Reductase Inhibitors (e.g., dutasteride, finasteride)	ATV/c, ATV/r, DRV/c, DRV/r	↑ dutasteride possible ↑ finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations. No dose adjustment needed for finasteride.
Testosterone	ATV/c, ATV/r, DRV/c, DRV/r	↑ testosterone possible	Adjust testosterone dose as needed based on clinical effects and endogenous hormone concentrations.
Other Gender-Affirming Medications	ATV/c, ATV/r, DRV/c, DRV/r	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Menopausal Hormone Replacement Therapy (e.g., conjugated estrogens, drospirenone, estradiol, MPA, progesterone)	ATV/c, ATV/r, DRV/c, DRV/r	↓ or ↑ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)	Adjust estrogen dose as needed based on clinical effects.
	ATV/c, ATV/r, DRV/c, DRV/r	↑ drospirenone possible ↑ MPA ↑ micronized progesterone See the Hormonal Therapies—Contraceptives section for other progestin-PI interactions.	Adjust progestin/progesterone dose as needed based on clinical effects. Drospirenone is not contraindicated with ATV/c products because it is prescribed at a lower dose for menopausal HRT than products used for hormonal contraceptives.
Immunosuppressants			
Cyclosporine, Sirolimus, Tacrolimus	ATV/c, ATV/r, DRV/c, DRV/r	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Everolimus	DRV/c, DRV/r	↑ immunosuppressant expected	**Do not coadminister.**
	ATV/c, ATV/r	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lipid-Modifying			
Atorvastatin	ATV/r	↑ atorvastatin possible	Administer the lowest effective atorvastatin dose while monitoring for adverse events.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold and C_{max} ↑ 18.9-fold	**Do not coadminister.**
	DRV/c	Atorvastatin AUC ↑ 3.9-fold and C_{max} ↑ 4.2-fold	Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
Fluvastatin	ATV/c, DRV/c	↑ fluvastatin expected	Administer the lowest effective fluvastatin dose while monitoring for adverse events.
	ATV/r, DRV/r	↑ or ↓ fluvastatin possible	
Lomitapide	ATV/c, ATV/r, DRV/c, DRV/r	↑ lomitapide expected	**Contraindicated**
Lovastatin	ATV/c, ATV/r, DRV/c, DRV/r	Significant ↑ lovastatin expected	**Contraindicated**
Pitavastatin	ATV/c, DRV/c	No data	No dose adjustment needed. Monitor for pitavastatin-related adverse events.
	ATV/r, DRV/r	**With ATV/r** • ↔ pitavastatin expected • ↔ ATV/r expected **With DRV/r** • ↓ pitavastatin AUC 26% • ↔ DRV/r	No dose adjustment needed

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Pravastatin	ATV/c, ATV/r	No data	Administer the lowest effective pravastatin dose while monitoring for adverse events.
	DRV/c, DRV/r	**With DRV/r** • Pravastatin AUC ↑ 81% following single dose of pravastatin • Pravastatin AUC ↑ 23% at steady state	Administer the lowest effective pravastatin dose while monitoring for adverse events.
Rosuvastatin	ATV/r	Rosuvastatin AUC ↑ 3-fold and C_{max} ↑ 7-fold	Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 10 mg daily.
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold and C_{max} ↑ 10.6-fold	
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold and C_{max} ↑ 3.8-fold	Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 20 mg daily.
	DRV/r	Rosuvastatin AUC ↑ 48% and C_{max} ↑ 2.4-fold	Administer the lowest effective rosuvastatin dose while monitoring for adverse events.
Simvastatin	ATV/c, ATV/r, DRV/c, DRV/r	Significant ↑ simvastatin expected	**Contraindicated**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 105%	Monitor for sedation and other signs or symptoms of overmedication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	DRV/r	↔ buprenorphine Norbuprenorphine (active metabolite) AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment needed. Monitor for buprenorphine-related adverse events. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ATV/c, DRV/c	↑ buprenorphine possible	Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Monitor for buprenorphine-related adverse events.
Fentanyl	ATV/c, ATV/r, DRV/c, DRV/r	↑ fentanyl possible	Monitor for fentanyl-related adverse events, including potentially fatal respiratory depression.
Lofexidine	ATV/c, ATV/r, DRV/c, DRV/r	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	ATV/c, DRV/c	No data	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Monitor for methadone-related adverse events.
	ATV/r, DRV/r	ATV/r and DRV/r ↓ R-methadone[d] AUC 16% to 18%	Opioid withdrawal is unlikely but may occur. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Oxycodone	ATV/c, ATV/r, DRV/c, DRV/r	↑ oxycodone expected	Monitor for opioid-related adverse events, including potentially fatal respiratory depression. Oxycodone dose reduction may be necessary.
Tramadol	ATV/c, ATV/r, DRV/c, DRV/r	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.
PDE5 Inhibitors			
Avanafil	ATV/c, ATV/r, DRV/c, DRV/r	RTV 600 mg twice daily (for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	**Do not coadminister.**

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sildenafil	ATV/c, ATV/r, DRV/c, DRV/r	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg twice daily ↑ sildenafil AUC 1,000%	**For Treatment of Erectile Dysfunction** • Start with sildenafil 25 mg every 48 hours and monitor for sildenafil-related adverse events. **Contraindicated** for treatment of PAH.
Tadalafil	ATV/c, ATV/r, DRV/c, DRV/r	RTV 200 mg twice daily ↑ tadalafil AUC 124%	**For Treatment of Erectile Dysfunction** *As-Needed Use* • Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for tadalafil-related adverse events. *Once-Daily Use* • Do not exceed tadalafil 2.5 mg once daily. Monitor for tadalafil-related adverse events. **For Treatment of PAH** *In Patients on a PI >7 Days* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil Who Require a PI* • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients Switching Between COBI and RTV* • Maintain tadalafil dose. **For Treatment of Benign Prostatic Hyperplasia** • Maximum recommended daily dose is tadalafil 2.5 mg per day. Monitor for tadalafil-related adverse events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Vardenafil	ATV/c, ATV/r, DRV/c, DRV/r	RTV 600 mg twice daily ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for vardenafil-related adverse events.
Sedative/Hypnotics			
Benzodiazepines			
Alprazolam, Clonazepam, Diazepam	ATV/c, ATV/r, DRV/c, DRV/r	↑ benzodiazepine possible RTV 200 mg twice daily (for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248%	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
Lorazepam, Oxazepam, Temazepam	ATV/c, ATV/r, DRV/c, DRV/r	No data	These benzodiazepines are metabolized via non-CYP450 pathways and, therefore, have less interaction potential than other benzodiazepines.
Midazolam	ATV/c, ATV/r, DRV/c, DRV/r	↑ midazolam expected	Oral midazolam is **contraindicated** with PIs. Parenteral midazolam can be used with caution when given in a monitored situation with appropriate medical management available in case of respiratory sedation and/or prolonged sedation. Consider dose reduction, especially if more than a single dose of midazolam is administered.
Triazolam	ATV/c, ATV/r, DRV/c, DRV/r	↑ triazolam expected RTV 200 mg twice daily ↑ triazolam half-life 1,200% and ↑ AUC 2,000%	**Contraindicated**
Orexin Receptor Antagonist			
Daridorexant, Lemborexant, Suvorexant	ATV/c, ATV/r, DRV/c, DRV/r	↑ daridorexant, lemborexant, suvorexant expected	**Do not coadminister.**

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Other Sedatives			
Eszopiclone	ATV/c, ATV/r, DRV/c, DRV/r	↑ eszopiclone expected	Start with lowest dose and increase to a maximum of 2 mg daily; monitor for eszopiclone-related adverse events.
Zolpidem	ATV/c, ATV/r, DRV/c, DRV/r	↑ zolpidem possible	Initiate zolpidem at a low dose and monitor for zolpidem-related adverse events. Dose reduction may be necessary.
Miscellaneous			
Calcifediol	ATV/c, ATV/r, DRV/c, DRV/r	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored.
Cisapride	ATV/c, ATV/r, DRV/c, DRV/r	↑ cisapride expected	**Contraindicated**
Colchicine	ATV/c, ATV/r, DRV/c, DRV/r	RTV 100 mg twice daily ↑ colchicine AUC 296% and C_{max} ↑ 184% Significant ↑ colchicine expected with all PIs, with or without COBI or RTV	**For Treatment of Gout Flares** • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. **For Prophylaxis of Gout Flares** • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. **For Treatment of Familial Mediterranean Fever** • Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg twice daily. **Contraindicated** in patients with hepatic (Child-Pugh Score A, B, or C) or renal impairment (CrCl <60 mL/min)
Dronabinol	ATV/c, ATV/r, DRV/c, DRV/r	↑ dronabinol possible	Monitor for dronabinol-related adverse events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Eluxadoline	ATV/c, ATV/r, DRV/c, DRV/r	↑ eluxadoline expected	Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse events.
Finerenone	ATV/c, ATV/r, DRV/c, DRV/r	↑ finerenone expected	**Contraindicated**
Flibanserin	ATV/c, ATV/r, DRV/c, DRV/r	↑ flibanserin expected	**Contraindicated**
Naloxegol	ATV/c, ATV/r, DRV/c, DRV/r	↑ naloxegol expected	**Contraindicated**
Praziquantel	ATV/c, ATV/r, DRV/c, DRV/r	↑ praziquantel possible	Consider alternative ARV. If coadministration is necessary, monitor for praziquantel-related adverse events.

[a] DHA is an active metabolite of artemether and artesunate.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations also may be available.

[c] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl. Generic formulations also may be available.

[d] R-methadone is the active form of methadone.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CCB = calcium channel blocker; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CMV = cytomegalovirus; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DVT = deep vein thrombosis; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EVG/c = elvitegravir/cobicistat; GI = gastrointestinal; H2RA = H2 receptor antagonist; HCV = hepatitis C virus; HRT = hormone replacement therapy; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PE = pulmonary embolism; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; VPA = valproic acid

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Updated: September 12, 2024
Reviewed: September 12, 2024

This table provides information on the known or predicted interactions between non-nucleoside reverse transcriptase inhibitors (NNRTIs) and non-antiretroviral drugs. Cabotegravir (CAB) intramuscular (IM) plus rilpivirine (RPV) IM are co-packaged into a single product and are coadministered as a complete regimen; therefore, the dosing recommendations and clinical comments reflect the combination of CAB IM and RPV IM treatments. Drug interaction studies were not conducted with either CAB IM or RPV IM. Drug interaction studies with oral CAB and RPV were leveraged to make the dosing recommendations for CAB IM and RPV IM. For information regarding interactions between NNRTIs and other antiretroviral (ARV) drugs, including dosing recommendations, refer to Tables 24c, 24e, 24f, 25a, and 25b.

Recommendations for managing a particular drug interaction may differ, depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. When an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication.

Oral doses of RPV at 75 mg and 300 mg once daily (equivalent to 3 and 12 times the recommended dose) were associated with prolonged QTc (or QT corrected for heart rate) interval. Known and expected/theoretical pharmacokinetic interactions, resulting in increased RPV exposures, are included in this table due to the safety concern of QTc prolongation. There is limited information about the potential for pharmacodynamic interactions between RPV (in the absence of increased RPV exposures) and drugs that prolong the QTc interval; therefore, these are not included in this table.

Nevirapine (NVP) is no longer commonly used in clinical practice in the United States and is not included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions between NVP and concomitant medications. Information may also be found in archived versions of this guideline.

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	DOR, EFV	↔ NNRTI AUC	No dose adjustment needed
	ETR	↔ ETR expected	No dose adjustment needed
	RPV IM	↔ RPV expected	No dose adjustment needed
	RPV PO	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	DOR	↔ DOR expected	No dose adjustment needed
	EFV	↔ EFV AUC	No dose adjustment needed
	ETR	↔ ETR AUC	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RPV IM	↔ RPV expected	No dose adjustment needed
	RPV PO	RPV AUC ↓ 76% when famotidine 40 mg is taken 2 hours prior	Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.
Proton Pump Inhibitors	DOR	↔ DOR AUC and C_{min}	No dose adjustment needed
	EFV	↔ EFV expected	
	ETR	**With Omeprazole 40 mg Daily** • ETR AUC ↑ 41%	
	RPV IM	↔ RPV expected	No dose adjustment needed
	RPV PO	**With Omeprazole 20 mg Daily** • RPV AUC ↓ 40% to 65% and C_{min} ↓ 33%	**Contraindicated**
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin, Doxazosin, Silodosin, Terazosin	DOR, RPV IM, RPV PO	↔ alpha-adrenergic antagonists expected	No dose adjustment needed
	EFV, ETR	↓ alpha-adrenergic antagonists expected	Consider alternative ARV or alpha-antagonist therapy. If coadministration is necessary, monitor for therapeutic effectiveness of alpha antagonist.
Tamsulosin	DOR, RPV IM, RPV PO	↔ tamsulosin expected	No dose adjustment needed
	EFV, ETR	↓ tamsulosin expected	Monitor for therapeutic effectiveness of tamsulosin after 2–4 weeks. May need to increase dose to tamsulosin 0.8 mg once daily for patients who fail to respond to the 0.4-mg dose.
Antibacterials—Antimycobacterials			
Bedaquiline	DOR, RPV IM, RPV PO	↔ bedaquiline expected	No dose adjustment needed
	EFV, ETR	↓ bedaquiline possible	**Do not coadminister.**
Rifabutin	DOR	DOR AUC ↓ 50%	Increase DOR dose to 100 mg twice daily. No dose adjustment is needed for rifabutin.
	EFV	Rifabutin ↓ 38%	Increase rifabutin dose to 450–600 mg per day.
	ETR	↔ rifabutin and metabolite AUC ETR AUC ↓ 37%	**Do not coadminister** ETR plus PI/r with rifabutin. Use rifabutin 300 mg once daily if ETR is administered without PI/r.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RPV IM	↓ RPV expected	**Contraindicated**
	RPV PO	**Rifabutin Plus RPV 50 mg PO Once Daily Compared to RPV 25 mg Once Daily Alone** • ↔ RPV AUC and C_{min}	Increase RPV dose to 50 mg PO once daily during coadministration. No dose adjustment for rifabutin is needed.
Rifampin	DOR	DOR AUC ↓ 88%	**Contraindicated.** After stopping rifampin, wait 4 weeks before initiating DOR**.**
	EFV	EFV AUC ↓ 26%	**Do not use** EFV 400 mg with rifampin. Maintain EFV dose at 600 mg once daily and monitor for virologic response.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	RPV IM	↓ RPV possible	**Contraindicated**
	RPV PO	RPV AUC ↓ 80%	**Contraindicated**
Rifapentine	DOR	**Once-Weekly Rifapentine Plus Isoniazid and DOR 100 mg Twice Daily Compared to DOR 100 mg Twice Daily Alone** • DOR AUC ↓ 29%, C_{min} ↓ 31%	**Contraindicated.** After stopping rifapentine, wait 4 weeks before initiating DOR**.**
	EFV	**Daily Rifapentine (Max 600 mg) With EFV** • ↔ EFV **Weekly Rifapentine (Max 900 mg) With EFV** • ↔ EFV	No dose adjustment needed
	ETR	↓ ETR possible	**Do not coadminister.**
	RPV IM, RPV PO	↓ RPV possible	**Contraindicated**
Antibacterials—Macrolides			
Azithromycin	DOR, EFV, ETR, RPV IM, RPV PO	↔ azithromycin expected	No dose adjustment needed
Clarithromycin	DOR	↔ clarithromycin expected ↑ DOR possible	Monitor for ARV tolerability if used in combination.
	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness, or consider alternative agent (e.g., azithromycin) for MAC prophylaxis and treatment.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ETR	Clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment.
	RPV IM, RPV PO	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment. If coadministered, monitor for QTc prolongation.
Erythromycin	DOR	↑ DOR possible	Monitor for ARV tolerability if used in combination.
	EFV, ETR	↑ EFV and ETR possible ↓ erythromycin possible	Monitor for ARV tolerability and antibiotic efficacy if used in combination.
	RPV IM, RPV PO	↑ RPV possible	Consider alternative macrolide (e.g., azithromycin). If coadministered, monitor for QTc prolongation.
Anticoagulants			
Apixaban	DOR, RPV IM, RPV PO	↔ apixaban expected	No dose adjustment needed
	EFV, ETR	↓ apixaban possible	Consider alternative ARV or anticoagulant therapy.
Dabigatran, Edoxaban	DOR, EFV, ETR, RPV IM, RPV PO	↔ DOAC expected	No dose adjustment needed
Rivaroxaban	DOR, RPV IM, RPV PO	↔ rivaroxaban expected	No dose adjustment needed
	EFV, ETR	↓ rivaroxaban possible	Consider alternative ARV or anticoagulant therapy.
Warfarin	DOR, RPV IM, RPV PO	↔ warfarin expected	No dose adjustment needed
	EFV, ETR	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Antiseizure			
Carbamazepine, Phenobarbital, Phenytoin, Primidone	DOR	↓ DOR possible	**Contraindicated.** After stopping antiseizure medication, wait 4 weeks before initiating DOR.
	EFV	**Carbamazepine Plus EFV** • Carbamazepine AUC ↓ 27%	Consider alternative ARV or antiseizure medication. If coadministration is necessary, monitor antiseizure drug and EFV concentrations.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		• EFV AUC ↓ 36% **Phenytoin Plus EFV** • ↓ EFV • ↑ or ↓ phenytoin possible **Phenobarbital or Primidone Plus EFV** • ↓ EFV and antiseizure agent possible	
	ETR	↓ antiseizure agent and ETR possible	**Do not coadminister.**
	RPV IM, RPV PO	↓ RPV possible	**Contraindicated**
Eslicarbazepine	DOR, EFV, ETR, RPV IM, RPV PO	↓ NNRTI possible	Consider alternative ARV or antiseizure medication. If coadministration is necessary, monitor virologic response and consider monitoring plasma concentrations of ARVs.
Oxcarbazepine	DOR, RPV IM, RPV PO	↓ NNRTI possible	**Contraindicated**
	EFV, ETR	↓ NNRTI possible	Consider alternative ARV or antiseizure medication. If coadministration is necessary, monitor virologic response and consider monitoring plasma concentrations of ARVs.
Ethosuximide, Lacosamide, Tiagabine, Zonisamide	DOR, RPV IM, RPV PO	↔ antiseizure agent expected	No dose adjustment needed
	EFV, ETR	↓ antiseizure agent possible	Monitor seizure control. Consider anticonvulsant therapeutic drug monitoring.
Lamotrigine	DOR, ETR, RPV IM, RPV PO	↔ lamotrigine expected	No dose adjustment needed
	EFV	↓ lamotrigine possible	Monitor seizure control and plasma concentrations of lamotrigine.
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below.			
Antidepressants and Anxiolytics			
Bupropion	DOR, ETR, RPV IM, RPV PO	↔ bupropion expected	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Citalopram, Escitalopram	DOR, RPV IM, RPV PO	↔ antidepressant expected	No dose adjustment needed
	EFV, ETR	↓ antidepressant possible	Titrate antidepressant dose based on clinical response.
Desvenlafaxine, Venlafaxine	DOR, EFV, ETR, RPV IM, RPV PO	↔ antidepressant expected	No dose adjustment needed
Duloxetine	DOR, EFV, ETR, RPV IM, RPV PO	↔ antidepressant expected	No dose adjustment needed
Fluoxetine, Fluvoxamine	DOR, EFV, ETR, RPV IM, RPV PO	↔ antidepressant expected	No dose adjustment needed
Mirtazapine	DOR, RPV IM, RPV PO	↔ mirtazapine expected	No dose adjustment needed
	EFV, ETR	↓ mirtazapine possible	Monitor antidepressant effect. Titrate dose as necessary based on clinical response.
Nefazodone	DOR, RPV IM, RPV PO	↑ NNRTI possible	No dose adjustment needed
	EFV, ETR	↓ nefazodone expected ↑ NNRTI possible	Monitor antidepressant effect. Titrate dose as necessary based on clinical response.
Paroxetine	DOR, ETR, RPV IM, RPV PO	↔ paroxetine expected	No dose adjustment needed
	EFV	↔ EFV and paroxetine	No dose adjustment needed
Sertraline	DOR, RPV IM, RPV PO	↔ sertraline expected	No dose adjustment needed
	EFV	Sertraline AUC ↓ 39%	Monitor the antidepressant effect. Titrate dose as necessary based on clinical response.
	ETR	↓ sertraline possible	

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Trazodone	DOR, RPV IM, RPV PO	↔ trazodone expected	No dose adjustment needed
	EFV, ETR	↓ trazodone possible	Monitor for therapeutic effectiveness of trazodone and titrate dose as necessary.
Tricyclic Antidepressants (e.g., amitriptyline, doxepin, nortriptyline)	DOR, EFV, ETR, RPV IM, RPV PO	↔ antidepressant expected	No dose adjustment needed
Antipsychotics			
Aripiprazole	DOR, RPV IM, RPV PO	↔ aripiprazole expected	No dose adjustment needed
	EFV, ETR	↓ aripiprazole expected	Monitor for therapeutic effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks. Refer to aripiprazole prescribing information for dose recommendations.
Brexpiprazole	DOR, RPV IM, RPV PO	↔ brexpiprazole expected	No dose adjustment needed
	EFV, ETR	↓ brexpiprazole expected	Monitor for therapeutic effectiveness of antipsychotic. Consider doubling the usual dose of brexpiprazole and making further adjustments based on clinical response. Refer to brexpiprazole prescribing information.
Cariprazine	DOR, RPV IM, RPV PO	↔ cariprazine expected	No dose adjustment needed
	EFV, ETR	↓ cariprazine and ↑ or ↓ active metabolite possible	**Do not coadminister.**
Iloperidone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed
	EFV, ETR	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Lumateperone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed
	EFV, ETR	↓ antipsychotic possible	**Do not coadminister.**

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lurasidone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed
	EFV, ETR	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Olanzapine, Olanzapine/Samidorphan	DOR, ETR, RPV IM, RPV PO	↔ olanzapine expected	No dose adjustment needed
	EFV	↓ olanzapine possible	Monitor for therapeutic effectiveness of olanzapine.
Other Antipsychotics **CYP3A4 Substrates** (e.g., clozapine, haloperidol, perphenazine, risperidone, thioridazine)	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed
	EFV, ETR	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Pimavanserin	DOR, RPV IM, RPV PO	↔ pimavanserin expected	No dose adjustment needed
	EFV, ETR	↓ pimavanserin expected	**Do not coadminister.**
Pimozide	DOR, RPV IM, RPV PO	↔ pimozide expected	No dose adjustment needed
	EFV, ETR	↓ pimozide possible	Monitor for therapeutic effectiveness of pimozide.
Quetiapine	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed
	EFV, ETR	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Ziprasidone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed
	EFV, ETR	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Antifungals			
Fluconazole	DOR	↑ DOR possible	No dose adjustment needed
	EFV	↔ fluconazole expected ↔ EFV AUC	No dose adjustment needed
	ETR	ETR AUC ↑ 86%	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Ibrexafungerp	DOR, RPV PO	↑ NNRTI possible	No dose adjustment needed
	EFV, ETR	↓ ibrexafungerp expected ↑ NNRTI possible	**Do not coadminister.**
	RPV IM	↔ ibrexafungerp expected ↔ RPV IM expected	No dose adjustment needed
Isavuconazole	DOR	↑ DOR possible	No dose adjustment needed
	EFV, ETR	↓ isavuconazole possible	Monitor isavuconazole concentration and antifungal response. Dose adjustments for isavuconazole may be necessary.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Itraconazole	DOR	↑ DOR possible	No dose adjustment needed
	EFV	**EFV With Itraconazole Solution** • Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 37% to 44% **EFV With Itraconazole Capsules** • Itraconazole AUC ↓ 86% and OH-itraconazole AUC 84%	**Do not coadminister** unless potential benefits outweigh the risks. Failure to achieve therapeutic itraconazole concentrations has been reported. If coadministration is necessary, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole concentration and antifungal response.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Posaconazole	DOR, ETR	↑ NNRTI possible	No dose adjustment needed
	EFV	Posaconazole AUC ↓ 50% ↔ EFV AUC	**Do not coadminister** unless potential benefits outweigh the risks. If coadministration is necessary, monitor posaconazole concentration and adjust dose accordingly.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Voriconazole	DOR	↑ DOR possible	No dose adjustment needed
	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses** Adjust dose to voriconazole 400 mg twice daily plus EFV 300 mg daily.
	ETR	↔ voriconazole AUC ETR AUC ↑ 36%	No dose adjustment needed
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Antimalarials			
Artemether/Lumefantrine	DOR, RPV IM, RPV PO	↔ antimalarial expected	No dose adjustment needed
	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 30% to 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy.
	ETR	Artemether AUC ↓ 38% ↔ DHA AUC ↔ lumefantrine AUC ↔ ETR AUC	Clinical significance of the reduced antimalarial drug concentrations is unknown. If used in combination with ETR, monitor for antimalarial efficacy.
Atovaquone/Proguanil	DOR, ETR, RPV IM, RPV PO	No data	Monitor for antimalarial efficacy.
	EFV	Atovaquone AUC ↓ 75% Proguanil AUC ↓ 43%	No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimigraine			
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists			
Atogepant	DOR RPV IM, RPV PO	↔ atogepant expected	No dose adjustment needed
	EFV, ETR,	↓ atogepant possible	Episodic migraine: Increase atogepant dose to 30–60 mg once daily. Chronic migraine: **Do not coadminister.**

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rimegepant	DOR, RPV IM, RPV PO	↔ rimegepant expected	No dose adjustment needed
	EFV, ETR,	↓ rimegepant possible	Consider alternative ARV or migraine medication.
Ubrogepant	DOR, RPV IM, RPV PO	↔ ubrogepant expected	No dose adjustment needed
	EFV, ETR	↓ ubrogepant expected	Use initial dose of 100 mg, followed by second dose of 100 mg if needed.
Zavegepant	DOR, RPV IM, RPV PO	↔ zavegepant expected	No dose adjustment needed
	EFV, ETR,	↓ zavegepant possible	
Serotonin 5-HT1B, 1D Receptor Agonists			
Almotriptan, Eletriptan	DOR RPV IM, RPV PO	↔ almotriptan expected	No dose adjustment needed
	EFV, ETR,	↓ almotriptan possible	
Frovatriptan, Naratripan, Rizatriptan, Sumatriptan, Zolmitriptan	DOR, EFV, ETR, RPV IM, RPV PO	↔ migraine medication expected	No dose adjustment needed
Antiplatelets			
Clopidogrel	DOR, RPV IM, RPV PO	↔ clopidogrel expected	No dose adjustment needed
	EFV, ETR	↓ activation of clopidogrel possible	Consider alternative ARV or antiplatelet. ETR may prevent metabolism of clopidogrel to its active metabolite.
Prasugrel	All NNRTIs	↔ prasugrel expected	No dose adjustment needed
Ticagrelor	DOR, RPV IM, RPV PO	↔ ticagrelor expected	No dose adjustment needed
	EFV, ETR	↓ ticagrelor expected	Consider alternative ARV or anticoagulant therapy.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Vorapaxar	DOR, RPV IM, RPV PO	↔ vorapaxar expected	No dose adjustment needed
	EFV, ETR	↓ vorapaxar expected	Insufficient data to make a dose recommendation.
Antipneumocystis and Antitoxoplasmosis			
Atovaquone (oral solution)	DOR, ETR, RPV IM, RPV PO	No data	Monitor for therapeutic effectiveness of atovaquone.
	EFV	Atovaquone AUC ↓ 44% to 47%	Consider alternative ARV or agent for PCP or toxoplasmosis treatment or prophylaxis. If coadministration is necessary, monitor for therapeutic effectiveness of atovaquone.
Antivirals—Hepatitis C			
Elbasvir/Grazoprevir	DOR	↔ elbasvir and grazoprevir DOR AUC ↑ 56% and C_{min} ↑ 41%	No dose adjustment needed
	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓ 83% ↔ EFV	**Contraindicated**
	ETR	↓ elbasvir and grazoprevir expected	**Do not coadminister.**
	RPV IM	↔ elbasvir and grazoprevir expected ↔ RPV expected	No dose adjustment needed
	RPV PO	↔ elbasvir and grazoprevir ↔ RPV AUC and C_{min}	No dose adjustment needed
Glecaprevir/Pibrentasvir	DOR	↑ DOR expected	No dose adjustment needed
	EFV	↓ glecaprevir and pibrentasvir expected	**Do not coadminister.**
	ETR	↓ glecaprevir and pibrentasvir possible	**Do not coadminister.**
	RPV IM	↔ glecaprevir and pibrentasvir expected ↑ RPV expected	No dose adjustment needed
	RPV PO	↔ glecaprevir and pibrentasvir RPV AUC ↑ 84%	No dose adjustment needed
Ledipasvir/Sofosbuvir	DOR	↔ ledipasvir and sofosbuvir ↔ DOR	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EFV	Ledipasvir AUC, C_{min}, and C_{max} ↓ 34% ↔ sofosbuvir	
	ETR	No significant effect expected	
	RPV IM	↔ ledipasvir, sofosbuvir, and RPV expected	
	RPV PO	↔ ledipasvir and sofosbuvir ↔ RPV	
Sofosbuvir/Velpatasvir	DOR, RPV IM, RPV PO	No significant effect expected	No dose adjustment needed
	EFV	Velpatasvir AUC ↓ 43%, C_{max} ↓ 37%, and C_{min} ↓ 47%	**Do not coadminister.**
	ETR	↓ velpatasvir expected	**Do not coadminister.**
Sofosbuvir/Velpatasvir/ Voxilaprevir	DOR, RPV IM, RPV PO	No significant effect expected	No dose adjustment needed.
	EFV	Velpatasvir AUC ↓ 43%, C_{max} ↓ 37%, and C_{min} ↓ 47% ↓ voxilaprevir expected	**Do not coadminister.**
	ETR	↓ voxilaprevir expected ↓ velpatasvir expected	**Do not coadminister.**
Antivirals—Miscellaneous (e.g., for CMV, Mpox)			
Brincidofovir	All NNRTIs	↔ brincidofovir expected	No dose adjustment needed
Cidofovir	All NNRTIs	↔ cidofovir expected	No dose adjustment needed
Maribavir	DOR, RPV IM, RPV PO	↔ maribavir expected	No dose adjustment needed
	EFV, ETR	↓ maribavir possible	
Tecovirimat	DOR, RPV PO	↓ DOR or RPV expected but not likely to be clinically relevant	No dose adjustment needed
	EFV, ETR	↔ EFV or ETR expected	No dose adjustment needed
	RPV IM	↓ RPV expected but not likely to be clinically relevant	No dose adjustment needed. If there is a concern for suboptimal RPV exposure, seek expert consultation. Do not initiate CAB/RPV IM during or within 2 weeks after tecovirimat treatment. (Refer to Table 24d for interaction with CAB.)

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antivirals—SARS-CoV-2			
Molnupiravir	All NNRTIs	↔ expected	No dose adjustment needed
Remdesivir	All NNRTIs	↔ expected	No dose adjustment needed
Ritonavir-Boosted Nirmatrelvir	DOR	**With Ritonavir 100 mg Twice Daily** • DOR AUC ↑ 254%	No dose adjustment needed
	EFV, ETR, RPV PO, RPV IM	↔ expected	No dose adjustment needed
Cardiac Medications			
Beta-Blockers			
Atenolol, Metoprolol, Nebivolol	DOR, EFV, ETR, RPV IM, RPV PO	↔ beta-blocker expected	No dose adjustment needed
Bisoprolol, Carvedilol	DOR, RPV IM, RPV PO	↔ beta-blocker expected	No dose adjustment needed
	EFV, ETR	↓ beta-blocker possible	No dose adjustment needed. Monitor blood pressure and heart rate and titrate to clinical effect.
Labetalol	DOR, RPV IM, RPV PO	↔ beta-blocker expected	No dose adjustment needed
	EFV, ETR	↑ beta-blocker possible	No dose adjustment needed. Monitor blood pressure and heart rate and adjust dose to achieve desired clinical effect.
Calcium Channel Blockers			
Dihydropyridine Calcium Channel Blockers (e.g., amlodipine, nifedipine)	DOR, RPV IM, RPV PO	↔ CCBs expected	No dose adjustment needed
	EFV, ETR	↓ CCBs possible	Titrate CCB dose based on clinical response.
Non-Dihydropyridine Calcium Channel Blockers (e.g., diltiazem, verapamil)	DOR, RPV IM, RPV PO	↔ CCBs expected ↑ NNRTI possible	No dose adjustment needed
	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	ETR	↓ diltiazem or verapamil possible	

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac—Other			
Bosentan	DOR	↓ DOR possible	Consider alternative ARV or alternative to bosentan. If coadministration is necessary, monitor virologic response.
	EFV, ETR	↓ NNRTI possible ↓ bosentan possible	Consider alternative ARV or alternative to bosentan. If coadministration is necessary, monitor bosentan efficacy and virologic response.
	RPV IM, RPV PO	↓ RPV possible	Consider alternative ARV or alternative to bosentan. If coadministration is necessary, monitor virologic response.
Eplerenone	DOR, RPV IM, RPV PO	↔ eplerenone expected	No dose adjustment needed
	EFV, ETR	↓ eplerenone possible	Titrate eplerenone dose based on clinical response.
Ivabradine	DOR, RPV IM, RPV PO	↔ ivabradine expected	No dose adjustment needed
	EFV, ETR	↓ ivabradine expected	**Contraindicated**
Mavacamten	DOR, RPV IM, RPV PO	↔ mavacamten expected ↓ NNRTI possible	Consider alternative ARV or alternative to mavacamten. If coadministration is necessary, monitor virologic response.
	EFV, ETR	↓ mavacamten expected ↓ NNRTI possible	**Contraindicated**
Ranolazine	DOR, RPV IM, RPV PO	↔ ranolazine expected	No dose adjustment needed
	EFV, ETR	↓ ranolazine expected	**Contraindicated**
Corticosteroids			
Beclomethasone, Ciclesonide	DOR, EFV, ETR, RPV IM, RPV PO	↔ corticosteroid expected	No dose adjustment needed
Budesonide, Fluticasone, Mometasone	DOR, RPV IM, RPV PO	↔ corticosteroid expected	No dose adjustment needed
	EFV, ETR,	↓ corticosteroid possible	Monitor corticosteroid efficacy and titrate as needed. May consider alternative corticosteroid for long-term use.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Dexamethasone	DOR, EFV, ETR	↓ NNRTI possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV IM, RPV PO	Significant ↓ RPV possible	**Contraindicated** with more than a single dose of dexamethasone.
Prednisone, Prednisolone	DOR, RPV IM, RPV PO	↔ corticosteroid expected	No dose adjustment needed
	EFV, ETR,	↓ corticosteroid possible	Monitor corticosteroid efficacy and titrate as needed. May consider alternative corticosteroid for long-term use.
Glucose-Lowering			
Linagliptin, Sitagliptin	DOR, RPV IM, RPV PO	↔ antihyperglycemic expected	No dose adjustment needed
	EFV, ETR	↓ antihyperglycemic possible	Monitor glycemic control.
Metformin	DOR	↔ metformin AUC DOR AUC ↓ 26% and C_{max} ↓ 24%	No dose adjustment needed
	EFV, ETR, RPV IM	↔ metformin expected	No dose adjustment needed
	RPV PO	↔ metformin AUC	No dose adjustment needed
Sodium-Glucose Cotransporter-2 Inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin)	DOR, EFV, ETR, RPV IM, RPV PO	↔ antihyperglycemic expected	No dose adjustment needed
Herbal Products			
St. John's Wort	DOR	↓ DOR expected	**Contraindicated.** After stopping St. John's Wort, wait 4 weeks before initiating DOR.
	EFV, ETR	↓ EFV or ETR expected	**Do not coadminister.**
	RPV IM, RPV PO	↓ RPV expected	**Contraindicated**
Hormonal Therapies—Contraceptives			
Injectable Contraceptives Depot MPA	DOR, ETR, RPV IM, RPV PO	↔ MPA expected	No dose adjustment needed
	EFV	↔ MPA	No dose adjustment needed. Refer to Women With HIV section for people on EFV and RIF.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Oral Contraceptives (e.g., desogestrel, drospirenone, ethinyl estradiol, levonorgestrel, norgestimate)	DOR	↔ ethinyl estradiol ↔ levonorgestrel ↔ drospirenone expected	No dose adjustment needed
	EFV	↔ ethinyl estradiol Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 61% Levonorgestrel (metabolite of oral norgestimate) AUC ↓ 83% Norelgestromin (metabolite of oral norgestimate) AUC ↓ 64% ↓ drospirenone possible	**When Used for Contraception** Use alternative ARV or contraceptive methods. **When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation)** Monitor for clinical effectiveness of hormonal therapy.
	ETR	Ethinyl estradiol AUC ↑ 22% ↔ norethindrone ↓ drospirenone possible	No dose adjustment needed for regimens that do not contain drospirenone For drospirenone-containing regimens used for contraception, use alternative ARV or alternative contraceptive method. If using drospirenone for other clinical indications, monitor for clinical effectiveness of hormonal therapy.
	RPV IM	↔ ethinyl estradiol expected ↔ norethindrone expected ↔ drospirenone expected	No dose adjustment needed
	RPV PO	↔ ethinyl estradiol ↔ norethindrone ↔ drospirenone expected	No dose adjustment needed
Subdermal Implant Contraceptives (e.g., etonogestrel, levonorgestrel)	DOR, RPV IM, RPV PO	↔ etonogestrel expected ↔ levonorgestrel expected	No dose adjustment needed
	EFV	Etonogestrel AUC ↓ 63% to 82% Levonorgestrel AUC ↓ 42% to 47% **Levonorgestrel 300 mg Implant With 600 mg EFV Compared to Levonorgestrel 150 mg Implant** • Levonorgestrel AUC ↓ 34%	Use alternative ARV or contraceptive methods. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ETR	↓ etonogestrel possible ↓ levonorgestrel possible	Consider using alternative ARV or contraceptive methods.
Transdermal Contraceptives (e.g., ethinyl estradiol/norelgestromin, ethinyl estradiol/levonorgestrel)	DOR, RPV IM, RPV PO	↔ ethinyl estradiol or norelgestromin expected	No dose adjustment needed
	EFV	↓ ethinyl estradiol or norelgestromin possible	Consider alternative ARV or contraceptive method.
	ETR	↓ ethinyl estradiol or norelgestromin possible	Consider alternative ARV or contraceptive method.
Vaginal Ring Contraceptives (e.g., etonogestrel/ethinyl estradiol, segesterone/ethinyl estradiol)	DOR, RPV IM, RPV PO	↔ etonogestrel and ethinyl estradiol expected ↔ segesterone and ethinyl estradiol expected	No dose adjustment needed
	EFV	Ethinyl estradiol (intravaginal ring) AUC ↓ 56% Etonogestrel (intravaginal ring) AUC ↓ 81%	Use alternative ARV or contraceptive method.
		↓ segesterone and ethinyl estradiol possible	Consider alternative ARV or contraceptive method.
	ETR	↓ etonogestrel and ethinyl estradiol possible ↓ segesterone and ethinyl estradiol possible	Consider alternative ARV or contraceptive method.
Emergency Contraceptives Levonorgestrel (oral)	DOR, RPV IM, RPV PO	↔ levonorgestrel expected	No dose adjustment needed.
	EFV	**Levonorgestrel 1.5 mg Plus 600 mg EFV** • Levonorgestrel AUC ↓ 58% **Levonorgestrel 3 mg Plus 600 mg EFV Compared to Levonorgestrel 1.5 mg Alone** • ↔ levonorgestrel AUC	Increase dose of levonorgestrel to 3mg when used for emergency postcoital contraception.
	ETR	↓ levonorgestrel possible	Consider alternative ARV or contraceptive method.
Hormonal Therapies—Gender Affirming and Menopause			
Estradiol	DOR, RPV IM, RPV PO	↔ estradiol expected	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EFV	Estradiol AUC ↓ 28% ↔ EFV AUC	Monitor feminizing effects of estrogen and therapy. Titrate dose as necessary to achieve therapeutic goals
	ETR	↓ estradiol possible	
5-Alpha Reductase Inhibitors (e.g., dutasteride, finasteride)	DOR, RPV IM, RPV PO	↔ dutasteride and finasteride expected	No dose adjustment needed
	EFV, ETR	↓ dutasteride and finasteride possible	Monitor masculinizing effects of testosterone. Titrate testosterone dose as necessary to achieve therapeutic goals.
Testosterone	DOR, RPV IM, RPV PO	↔ testosterone expected	No dose adjustment needed
	EFV, ETR	↓ testosterone possible	Monitor masculinizing effects of testosterone. Titrate testosterone dose as necessary to achieve therapeutic goals.
Other Gender-Affirming Medications	DOR, RPV IM, RPV PO	↔ hormonal concentrations expected	No dose adjustment needed
	EFV, ETR	↓ cyproterone and progestogens possible ↔ goserelin, leuprolide acetate, and spironolactone expected	Monitor feminizing effects of estrogen and antiandrogen therapy. Titrate dose as necessary to achieve therapeutic goals.
Menopausal Hormone Replacement Therapy (e.g., conjugated estrogens, drospirenone, estradiol, medroxyprogesterone, progesterone)	DOR, RPV IM, RPV PO	↔ hormonal concentrations expected	No dose adjustment needed
	EFV, ETR	↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic) ↓ medroxyprogesterone possible ↓ micronized progesterone possible ↓ drospirenone possible See Contraceptives—Oral above for other progestin-NNRTI interactions	Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Immunosuppressants			
Cyclosporine	DOR, RPV IM, RPV PO	↔ cyclosporine expected ↑ NNRTI possible	No dose adjustment needed
	EFV, ETR	↓ cyclosporine possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Everolimus, Sirolimus, Tacrolimus	DOR, RPV IM, RPV PO	↔ immunosuppressant expected	No dose adjustment needed
	EFV, ETR	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Lipid-Modifying			
Atorvastatin	DOR	↔ atorvastatin AUC	No dose adjustment needed
	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	RPV IM	↔ atorvastatin expected	No dose adjustment needed
	RPV PO	↔ atorvastatin AUC	No dose adjustment needed
Fluvastatin	DOR, RPV IM, RPV PO	↔ fluvastatin expected	No dose adjustment needed
	EFV, ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin, Simvastatin	DOR, RPV IM, RPV PO	↔ lovastatin and simvastatin expected	No dose adjustment needed
	EFV	Simvastatin AUC ↓ 60% to 68% Simvastatin active metabolite AUC ↓ 60%	Adjust simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	ETR	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Pitavastatin	DOR, ETR, RPV IM, RPV PO	↔ pitavastatin expected	No dose adjustment needed
	EFV	↔ pitavastatin AUC	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Pravastatin	DOR, RPV IM, RPV PO	↔ pravastatin expected	No dose adjustment needed
	EFV	Pravastatin AUC ↓ 44%	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
	ETR	↓ pravastatin possible	
Rosuvastatin	DOR, EFV, ETR, RPV IM, RPV PO	↔ rosuvastatin expected	No dose adjustment needed
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual or buccal	DOR, RPV IM, RPV PO	↔ buprenorphine expected	No dose adjustment needed
	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine (active metabolite) AUC ↓ 71%	No dose adjustment needed, monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment needed
Buprenorphine Implant	DOR, RPV IM, RPV PO	↔ buprenorphine expected	No dose adjustment needed
	EFV, ETR	No data	Clinical monitoring is recommended when NNRTI is initiated after insertion of buprenorphine implant.
Lofexidine	DOR, EFV, ETR, RPV IM, RPV PO	↔ lofexidine expected	No dose adjustment needed
Methadone	DOR	↔ methadone AUC DOR AUC ↓ 26%	No dose adjustment needed
	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; monitor and increase methadone dose as necessary.
	ETR	↔ methadone AUC	No dose adjustment needed
	RPV IM	↓ methadone AUC expected	No dose adjustment needed; monitor for withdrawal symptoms.
	RPV PO	↔ R-methadone[a] AUC	No dose adjustment needed; monitor for withdrawal symptoms.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil, Tadalafil, Vardenafil	DOR, RPV IM, RPV PO	↔ PDE5 inhibitor expected	No dose adjustment needed
	EFV, ETR	↓ PDE5 inhibitor possible	May need to titrate dose based on clinical effect.
Sildenafil	DOR	↔ sildenafil expected	No dose adjustment needed
	EFV	↓ sildenafil possible	May need to titrate sildenafil dose based on clinical effect.
	ETR	Sildenafil AUC ↓ 57%	May need to titrate sildenafil dose based on clinical effect.
	RPV IM	↔ sildenafil expected	No dose adjustment needed
	RPV PO	↔ sildenafil AUC and C_{max}	No dose adjustment needed
Sedative/Hypnotics			
Benzodiazepines			
Alprazolam, Triazolam	DOR, RPV IM, RPV PO	↔ alprazolam or triazolam expected	No dose adjustment needed
	EFV, ETR	↓ alprazolam or triazolam possible	Monitor for therapeutic effectiveness of benzodiazepine.
Diazepam	DOR, RPV IM, RPV PO	↔ diazepam expected	No dose adjustment needed
	EFV	↓ diazepam possible	Monitor for therapeutic effectiveness of diazepam.
	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary. Monitor for diazepam toxicity.
Lorazepam	DOR, ETR, RPV IM, RPV PO	↔ lorazepam expected	No dose adjustment needed
	EFV	↔ lorazepam AUC	No dose adjustment needed
Midazolam	DOR	↔ midazolam AUC	No dose adjustment needed
	EFV	↑ or ↓ midazolam possible	Monitor for therapeutic effectiveness and toxicity of midazolam.
	ETR	Midazolam AUC ↓ 31% Midazolam active metabolite C_{max} ↑ 57%	Monitor for therapeutic effectiveness of midazolam.
	RPV IM, RPV PO	↔ midazolam expected	No dose adjustment needed

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Orexin Receptor Antagonists			
Daridorexant	DOR, RPV IM, RPV PO	↔ daridorexant expected	No dose adjustment needed
	EFV	Daridorexant AUC ↓ 61%	**Do not coadminister.**
	ETR	↓ daridorexant possible	
Lemborexant, Suvorexant	DOR, RPV IM, RPV PO	↔ lemborexant expected	No dose adjustment needed
	EFV, ETR	↓ lemborexant possible	**Do not coadminister.**
Other Sedatives			
Eszopiclone, Zolpidem	DOR, RPV IM, RPV PO	↔ eszopiclone or zolpidem expected	No dose adjustment needed
	EFV, ETR	↓ eszopiclone or zolpidem possible	Monitor for therapeutic effectiveness of sedative and titrate to clinical effect.
Miscellaneous			
Finerenone	DOR, RPV IM, RPV PO	↔ finerenone expected	No dose adjustment needed
	EFV, ETR	↓ finerenone expected	Consider alternative ARV or alternative to finerenone. If coadministration is necessary, monitor finerenone efficacy.
Praziquantel	DOR, RPV IM, RPV PO	↔ praziquantel expected	No dose adjustment needed
	EFV	R-praziquantel and S-praziquantel AUC ↓ 74% to 75%	**Do not coadminister**. If coadministration is necessary, consider alternative ARVs.
	ETR	↓ praziquantel possible	**Do not coadminister.** If coadministration is necessary, consider alternative ARVs.

[a] R-methadone is the active form of methadone.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: ARV = antiretroviral; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CAB = cabotegravir; CCB = calcium channel blocker; DAA = direct-acting antiviral; DHA = dihydroartemisinin; DOAC = direct oral anticoagulants; DOR = doravirine; EFV = efavirenz; ETR = etravirine; IM = intramuscular; INR = international normalized ratio; isoniazid = isonicotinic acid hydrazide; MAC = *Mycobacterium avium* complex; MPA = medroxyprogesterone acetate; CMV = cytomegalovirus; NNRTI = non-nucleoside reverse transcriptase inhibitor; OH-itraconazole = active metabolite of itraconazole; PCP = *Pneumocystis jirovecii* pneumonia; PDE5 = phosphodiesterase type 5; PI/r = protease inhibitor/ritonavir; PO = orally; QTc = QT corrected for heart rate; RPV = rilpivirine

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Updated: September 12, 2024
Reviewed: September 12, 2024

This table provides information on the known or predicted interactions between nucleoside reverse transcriptase inhibitors (NRTIs) and non-antiretroviral drugs.

Recommendations for managing a particular drug interaction may differ depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication.

This table focuses on interactions with pharmacokinetic study data and interactions without study data but where there is a clinical recommendation. Interactions associated with zidovudine (ZDV) are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions between ZDV and other drugs.

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials—Antimycobacterials			
Rifabutin	3TC, ABC, FTC,	↔ expected	No dose adjustment needed
	TAF	↓ TAF possible	**Use with caution.** If coadministered, monitor virologic response.
	TDF	↔ AUC TFV	No dose adjustment needed
Rifampin	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	**TAF With Rifampin Compared With TDF Alone** • TFV-DP AUC ↑ 4.2-fold **TAF With Rifampin Compared With TAF Alone** • TAF AUC ↓ 55% • TFV-DP AUC ↓ 36% **TAF 25 mg Twice Daily With Rifampin Compared With TAF Once Daily Alone** • TAF AUC ↓ 14% • TFV-DP AUC ↓ 24%	**Use with caution.** If coadministered, monitor virologic response. Intracellular TFV-DP levels are higher when TAF is coadministered with rifampin than when TDF is administered alone, but clinical outcomes have not been studied.
	TDF	↔ AUC TFV	No dose adjustment needed

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifapentine	3TC, ABC, FTC,	↔ expected	No dose adjustment needed
	TAF	↓ TAF possible	**Use with caution.** If coadministered, monitor virologic response.
	TDF	↔ AUC TFV	No dose adjustment needed
Antiseizure			
Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	ABC	↑ carbamazepine possible ↓ ABC possible with oxcarbazepine, phenobarbital, phenytoin	No dose adjustment needed
	3TC, FTC, TDF	↔ expected	No dose adjustment needed
	TAF	**With Carbamazepine** • TAF AUC ↓ 55% • ↓ TAF possible with other anticonvulsants	**Do not coadminister.**
Antivirals—Hepatitis C			
Glecaprevir/Pibrentasvir	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	↔ TFV AUC	No dose adjustment needed
	TDF	TFV AUC ↑ 29%	No dose adjustment needed
Ledipasvir/Sofosbuvir	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	TFV AUC ↑ 27%	No dose adjustment needed
	TDF	Ledipasvir ↑ TFV AUC 35% to 98% when TDF is given with various PIs and NNRTIs. Ledipasvir ↑ TFV C_{min} 55% to 80% when TDF is given with various PIs, NNRTIs, or INSTIs. Further ↑ TFV AUC and C_{max} possible when TDF, ledipasvir/sofosbuvir, and PIs are coadministered.	**Do not coadminister** with EVG/c, TDF, or FTC. If TDF is used, monitor for TDF toxicities. Consider using TAF in patients at risk of TDF-associated adverse events. Consider using TAF or alternative HCV therapy in patients on TDF plus a PI/r or PI/c. The safety of increased TFV exposure with this combination has not been established.
Ribavirin	3TC	↔ 3TC AUC	No dose adjustment needed
	ABC, FTC, TAF	↔ expected	No dose adjustment needed
	TDF	**Ribavirin With Sofosbuvir 400 mg** • ↔ TFV AUC	No dose adjustment needed

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sofosbuvir/Velpatasvir	3TC, ABC, FTC, TAF	↔ expected	No dose adjustment needed
	TDF	TFV C_{max} ↑ 44% to 46% and AUC ↑ 40% when coadministered with various ARV combinations.	If TDF is used in these patients, monitor for TDF-related toxicities. Consider using TAF in patients at risk of TDF-related adverse events.
Sofosbuvir/Velpatasvir/ Voxilaprevir	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	TAF AUC ↑ 52% to 57%	No dose adjustment needed
	TDF	TFV C_{max} ↑ 48% and AUC ↑ 39% when coadministered with various ARV combinations.	Monitor for TDF-related toxicities. Consider using TAF in patients at risk of TDF-related adverse events.
Antivirals—Miscellaneous (e.g., for Herpesvirus, CMV, HBV, Mpox)			
Adefovir	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	↑ TFV possible	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may increase.
	TDF	↔ TFV	**Do not coadminister.**
Brincidofovir	3TC, ABC, FTC, TAF, TDF	↔ brincidofovir expected	No dose adjustment needed
Cidofovir	3TC, ABC, FTC, TAF	↔ cidofovir expected	No dose adjustment needed
	TDF	↑ TDF and cidofovir possible	Potential for renal toxicity when TDF is given with a nephrotoxic agent, such as cidofovir. If concomitant use is necessary, closely monitor renal function.
Famciclovir	3TC, ABC, TAF, TDF	↔ expected	No dose adjustment needed
	FTC	↔ AUC FTC, famciclovir	No dose adjustment needed
Ganciclovir, Valganciclovir	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF, TDF	↑ ganciclovir or TFV possible	Monitor for dose-related toxicities.
Tecovirimat	3TC, ABC, FTC, TAF, TDF	↔ tecovirimat expected	No dose adjustment needed
Antivirals—SARS-CoV-2			
Molnupiravir	3TC, ABC, FTC, TAF, TDF	↔ expected	No dose adjustment needed
Remdesivir	3TC, ABC, FTC, TAF, TDF	↔ expected	No dose adjustment needed
Ritonavir-Boosted Nirmatrelvir	3TC, ABC, FTC, TAF, TDF	↔ expected	No dose adjustment needed

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies—Contraceptives			
Injectable Contraceptives Depot MPA	3TC, ABC, TAF	↔ expected	No dose adjustment needed
	FTC, TDF	↔ FTC AUC ↔ TFV AUC	No dose adjustment needed
Oral Contraceptives (e.g., desogestrel, drospirenone, ethinyl estradiol, levonorgestrel, norelgestromin, norgestimate, norgestrel)	3TC, ABC, FTC, TDF	↔ expected	No dose adjustment needed
	TAF	↔ ethinyl estradiol AUC ↔ norelgestromin AUC ↔ norgestrel AUC	No dose adjustment needed
Hormonal Therapies—Gender Affirming and Menopause			
Estradiol Valerate	3TC, ABC, TAF	↔ expected	No dose adjustment needed
	FTC	↔ FTC AUC ↔ estradiol AUC	
	TDF	↔ TFV AUC ↔ estradiol	
17-β-estradiol	3TC, ABC, TAF	↔ expected	No dose adjustment needed
	FTC	FTC AUC ↓ 14% to 24%	
	TDF	TFV AUC ↓ 12% to 27%	
Other Medications Used for Gender-Affirming Therapy or Menopausal Replacement Therapy	ABC, 3TC, FTC, TAF, TDF	↔ NRTI expected	No dose adjustment needed
Narcotics and Treatment for Opioid Dependence			
Buprenorphine	ABC, FTC	↔ expected	No dose adjustment needed
	3TC, TDF	↔ 3TC, TDF, and buprenorphine	No dose adjustment needed
	TAF	↔ TAF expected	No dose adjustment needed
Methadone	3TC, FTC, TAF, TDF	↔ expected	No dose adjustment needed
	ABC	Methadone clearance ↑ 22%	No dose adjustment needed

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous			
Ethanol	ABC	ABC AUC ↑ 41%	No dose adjustment needed
Riociguat	3TC, FTC, TAF, TDF	↔ expected	No dose adjustment needed
	ABC	Riociguat AUC ↑ 200%	If coadministered, initiate riociguat at 0.5 mg three times daily and monitor for riociguat-related adverse effects (e.g., hypotension).
St. John's Wort	3TC, ABC, FTC, TDF	↔ expected	No dose adjustment needed
	TAF	↓ TAF possible	**Do not coadminister.**
Antiretrovirals			
Capsid Inhibitor			
LEN (SQ and PO)	3TC, ABC, FTC	↔ 3TC, ABC, FTC, LEN expected	No dose adjustment needed
	TAF	TAF AUC ↑ 32% ↔ LEN	No dose adjustment needed
	TDF	TDF AUC ↑ 47% ↔ LEN	No dose adjustment needed
INSTIs			
DTG	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	↔ TAF AUC	No dose adjustment needed
	TDF	↔ TDF AUC ↔ DTG AUC	No dose adjustment needed
RAL	3TC, ABC, FTC, TAF	↔ expected	No dose adjustment needed
	TDF	RAL AUC ↑ 49%	No dose adjustment needed
PIs			
ATV/c, ATV/r	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	**TAF 10 mg With ATV/r** • TAF AUC ↑ 91% **TAF 10 mg With ATV/c** • TAF AUC ↑ 75%	No dose adjustment needed (use TAF 25 mg)

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	TDF	**With ATV (Unboosted)** • ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) • TFV AUC ↑ 24% to 37%	Use ATV 300 mg plus (RTV 100 mg or COBI 150 mg) daily when coadministering TDF 300 mg daily. If using TDF and an H2 receptor antagonist in an ART-experienced patient, use ATV 400 mg plus (RTV 100 mg or COBI 150 mg) daily. Monitor for TDF-associated toxicities.
DRV/c	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	**TAF 25 mg With DRV/c** • ↔ TAF	No dose adjustment needed
	TDF	TFV ↑ possible	Monitor for TDF-associated toxicities.
DRV/r	3TC, ABC, FTC	↔ expected	No dose adjustment needed
	TAF	**TAF 10 mg With DRV/r** • ↔ TAF AUC	No dose adjustment needed
	TDF	TFV AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance is unknown. If coadministered, monitor for TDF-associated toxicities.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CMV = cytomegalovirus; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; MPA = medroxyprogesterone acetate; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PO: oral; RAL = raltegravir; RTV = ritonavir; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Updated: September 12, 2024
Reviewed: September 12, 2024

This table provides information on the known or predicted interactions between integrase strand transfer inhibitors (INSTIs) (bictegravir [BIC], dolutegravir [DTG], elvitegravir [EVG], or raltegravir [RAL]) and non-antiretroviral drugs. EVG is always coadministered with cobicistat (COBI or c). Cabotegravir (CAB) intramuscular (IM) plus rilpivirine (RPV) IM are co-packaged into a single product and are coadministered as a complete regimen; therefore, the dosing recommendations and clinical comments reflect the combination of CAB IM and RPV IM treatments. Because drug interaction studies were not conducted with either IM CAB or RPV, dosing recommendations for the IM formulations are based on drug interaction studies using oral CAB and RPV. For information regarding interactions between INSTIs and other antiretroviral (ARV) drugs, including dosing recommendations, refer to Tables 24c, 24e, 24f, and 25b.

Recommendations for managing a particular drug interaction may differ, depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication.

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Al, Mg **+/–** **Ca-Containing Antacids** Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe and Ca supplements, multivitamins).	BIC	**Al/Mg Hydroxide Antacid** • ↔ BIC AUC if antacid is administered 2 hours after BIC and under fasting conditions • BIC AUC ↓ 52% if antacid is administered 2 hours before BIC • BIC AUC ↓ 47% to 79% if administered simultaneously with antacid **$CaCO_3$ Antacid** • ↔ BIC AUC if administered with food • BIC AUC ↓ 33% if administered under fasting conditions	**With Antacids That Contain Al/Mg** • Administer antacids that contain Al/Mg at least 2 hours after or 6 hours before BIC. **With Antacids That Contain Ca** • Administer BIC and antacids that contain Ca together with food. • **Do not coadminister** BIC simultaneously with antacids that contain Ca on an empty stomach.
	CAB PO	CAB PO ↓ expected	**With Antacids That Contain Polyvalent Cations (Al, Mg, or Ca)** • Administer antacid products at least 2 hours before or 4 hours after taking CAB PO.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	CAB IM	↔ CAB IM expected	No dose adjustment needed
	DTG	DTG AUC ↓ 74% if administered simultaneously with antacid DTG AUC ↓ 26% if administered 2 hours before antacid	Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations.
	EVG/c	EVG AUC ↓ 40% to 50% if administered simultaneously with antacid EVG AUC ↓ 15% to 20% if administered 2 hours before or after antacid; ↔ with a 4-hour interval	Separate EVG/c and antacid administration by more than 2 hours.
	RAL	**Al/Mg Hydroxide Antacid** • RAL C_{min} ↓ 49% to 63% **$CaCO_3$ Antacid** • RAL 400 mg twice daily: C_{min} ↓ 32% • RAL 1,200 mg once daily: C_{min} ↓ 48% to 57%	**Do not coadminister** RAL and Al/Mg hydroxide antacids. Use alternative acid-reducing agent. **With $CaCO_3$ Antacids** • RAL 1,200 mg once daily: **Do not coadminister.** • RAL 400 mg twice daily: No dose adjustment or separation needed
H2-Receptor Antagonists	BIC, CAB (PO and IM), DTG, EVG/c	↔ INSTI	No dose adjustment needed
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment needed
Proton Pump Inhibitors	BIC, CAB (PO and IM), DTG, EVG/c	↔ INSTI	No dose adjustment needed
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment needed
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, CAB (PO and IM), DTG, RAL	↔ alfuzosin expected	No dose adjustment needed
	EVG/c	↑ alfuzosin expected	**Contraindicated**
Doxazosin	BIC, CAB (PO and IM), DTG, RAL	↔ doxazosin expected	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose. Titrate based on doxazosin efficacy. Monitor blood pressure. Doxazosin dose reduction may be needed.
Tamsulosin	BIC, CAB (PO and IM), DTG, RAL	↔ tamsulosin expected	No dose adjustment needed
	EVG/c	↑ tamsulosin expected	**Do not coadminister** unless the benefits outweigh the risks. If coadministered, monitor blood pressure.
Terazosin	BIC, CAB (PO and IM), DTG, RAL	↔ terazosin expected	No dose adjustment needed
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose. Titrate based on terazosin efficacy. Monitor blood pressure. Terazosin dose reduction may be necessary.
Silodosin	BIC, CAB (PO and IM), DTG, RAL	↔ silodosin expected	No dose adjustment needed
	EVG/c	↑ silodosin expected	**Contraindicated**
Antibacterials—Antimycobacterials			
Bedaquiline	BIC, CAB (PO and IM), DTG, RAL	↔ bedaquiline	No dosage adjustment needed
	EVG/c	↑ bedaquiline possible	**Do not coadminister** unless benefits outweigh risks. If coadministered, consider therapeutic drug monitoring and monitor for bedaquiline-related adverse effects, including hepatotoxicity and QTc prolongation.
Rifabutin	BIC	**Rifabutin 300 mg Once Daily** • BIC AUC ↓ 38% and C_{min} ↓ 56%	**Do not coadminister.**
	CAB PO	CAB PO AUC ↓ 23% and C_{min} ↓ 26% ↔ rifabutin	No dose adjustment needed
	CAB IM	↓ CAB IM and RPV expected ↔ rifabutin expected	**Contraindicated** due to ↓ RPV, which is co-packaged and coadministered with CAB IM.
	DTG	**Rifabutin 300 mg Once Daily** • ↔ DTG AUC and C_{min} ↓ 30%	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	**Rifabutin 150 mg Every Other Day With EVG/c Once Daily Compared to Rifabutin 300 mg Once Daily Alone** • ↔ rifabutin AUC • 25-O-desacetyl-rifabutin AUC ↑ 625% • EVG AUC ↓ 21% and C_{min} ↓ 67%	**Do not coadminister.**
	RAL	↔ RAL AUC and C_{min} ↓ 20%	No dose adjustment needed
Rifampin	BIC	BIC AUC ↓ 75%	**Contraindicated**
	CAB PO	CAB PO AUC ↓ 59% and C_{min} ↓ 50%	**Contraindicated**
	CAB IM	CAB IM ↓ expected	**Contraindicated**
	DTG	**Rifampin With DTG 50 mg Twice Daily Compared to DTG 50 mg Twice Daily Alone** • DTG AUC ↓ 54% and C_{min} ↓ 72% **Rifampin With DTG 50 mg Twice Daily Compared to DTG 50 mg Once Daily Alone** • DTG AUC ↑ 33% and C_{min} ↑ 22%	Use DTG 50 mg twice daily (instead of DTG 50 mg once daily) in patients without suspected or documented INSTI-associated resistance mutations. Consider an alternative to rifampin, such as rifabutin, in patients with certain suspected or documented INSTI-associated resistance mutations.
	EVG/c	Significant ↓ EVG and COBI expected	**Contraindicated**
	RAL	**RAL 400 mg** • RAL AUC ↓ 40% and C_{min} ↓ 61% **Rifampin With RAL 800 mg Twice Daily Compared to RAL 400 mg Twice Daily Alone** • RAL AUC ↑ 27% and C_{min} ↓ 53%	Use RAL 800 mg twice daily instead of 400 mg twice daily. **Do not coadminister** RAL 1,200 mg once daily with rifampin. Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	BIC, EVG/c	Significant ↓ BIC, EVG, and COBI expected	**Do not coadminister.**
	CAB (PO and IM)	Significant ↓ CAB (PO and IM) expected	**Contraindicated**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	DTG	**Rifapentine 900 mg Once Weekly** • DTG AUC ↓ 26% and C_{min} ↓ 47% **Rifapentine 600 mg Once Daily With DTG 50 mg Twice Daily vs DTG 50 mg Once Daily Alone** • ↔ DTG AUC and C_{min}	With **once-weekly** rifapentine, DTG 50 mg daily may be used in patients with viral suppression on daily DTG. Monitor for virologic efficacy. **Do not coadminister** in patients who require twice-daily DTG. With **once-daily** rifapentine for 4 weeks (1HP), use DTG 50 mg twice daily. See Tuberculosis/HIV Coinfection for more on rifapentine and DTG use.
	RAL	**Rifapentine 900 mg Once Weekly** • RAL AUC ↑ 71% and C_{min} ↓ 12% **Rifapentine 600 mg Once Daily** • RAL C_{min} ↓ 41%	For once-weekly rifapentine and RAL 400 mg twice daily, no dose adjustment is needed. **Do not coadminister** with once-daily rifapentine.
Antibacterials—Macrolides			
Azithromycin	All INSTIs	↔ azithromycin expected	No dose adjustment needed
Clarithromycin	BIC	↑ BIC possible	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ clarithromycin expected	No dose adjustment needed
	EVG/c	↑ clarithromycin expected ↑ COBI possible	Reduce clarithromycin dose by 50% in patients with CrCl 50 to 60 mL/min. **Do not coadminister** in patients with CrCl <50 mL/min. Consider alternative ARV or use azithromycin.
Erythromycin	BIC	↑ BIC possible	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ erythromycin expected	No dose adjustment needed
	EVG/c	↑ erythromycin expected ↑ COBI possible	No data available for dose recommendation. Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	BIC, CAB (PO and IM), DTG, RAL	↔ apixaban expected	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ apixaban expected	**Do not coadminister** in patients who require apixaban 2.5 mg twice daily. Reduce apixaban dose by 50% in patients who require apixaban 5 mg or 10 mg twice daily.
Dabigatran	BIC, CAB (PO and IM), DTG, RAL	↔ dabigatran expected	No dose adjustment needed
	EVG/c	↑ dabigatran expected **With COBI 150 mg Alone** • Dabigatran AUC ↑ 110% to 127%	**Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation in Adult Patients** • CrCl >30 mL/min: no dose adjustment needed • CrCl ≤30 mL/min: **do not coadminister.** **Treatment and Reduction in the Risk of Recurrence of DVT and PE or Prophylaxis of DVT and PE Following Hip Replacement Surgery in Adult Patients** • CrCl ≥50 mL/min: no dose adjustment needed • CrCl <50 mL/min: **do not coadminister.**
Edoxaban	BIC, CAB (PO and IM), DTG, RAL	↔ edoxaban expected	No dose adjustment needed
	EVG/c	↑ edoxaban expected	**Stroke Prevention in Nonvalvular Atrial Fibrillation** • No dose adjustment needed **DVT and PE** • Administer edoxaban 30 mg once daily.
Rivaroxaban	BIC, CAB (PO and IM), DTG, RAL	↔ rivaroxaban expected	No dose adjustment needed
	EVG/c	↑ rivaroxaban expected	**Do not coadminister.**
Warfarin	BIC, CAB (PO and IM), DTG, RAL	↔ warfarin expected	No dose adjustment needed
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Antiseizure			
Carbamazepine	BIC	↓ BIC possible	**Do not coadminister.**
	CAB (PO and IM)	↓ CAB expected	**Contraindicated**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg twice daily in ART-naive or ART-experienced (but INSTI-naive) patients. **Do not coadminister** in INSTI-experienced patients with known or suspected INSTI resistance.
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated**
	RAL	↓ or ↔ RAL possible	**Do not coadminister.**
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider alternative ARV or anticonvulsant.
Ethosuximide	BIC, CAB (PO and IM), DTG, RAL	↔ ethosuximide expected	No dose adjustment needed
	EVG/c	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	BIC, CAB (PO and IM), DTG, RAL	↔ lamotrigine expected	No dose adjustment needed
	EVG/c	No data	Monitor anticonvulsant concentrations and adjust dose accordingly.
Oxcarbazepine	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	CAB (PO and IM)	↓ CAB expected	**Contraindicated**
	EVG/c, RAL	↓ EVG/c and RAL possible	Consider alternative ARV or anticonvulsant.
Phenobarbital, Phenytoin, Primidone	BIC, DTG, RAL	↓ BIC and DTG possible ↓ or ↔ RAL possible	**Do not coadminister.**
	CAB (PO and IM), EVG/c	↓ CAB and EVG/c expected	**Contraindicated**
Valproic Acid	DTG	DTG ↓ possible	No dose adjustment needed. Take with food and monitor virologic response.
	BIC, CAB (PO and IM), RAL	No data	No dose adjustment needed. Monitor virologic response.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below			
Antidepressants, Anxiolytics			
Bupropion	BIC, CAB (PO and IM), DTG, RAL	↔ bupropion expected	No dose adjustment needed
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, CAB (PO and IM), DTG, RAL	↔ buspirone expected	No dose adjustment needed
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Buspirone dose reduction may be needed.
Desvenlafaxine	All INSTIs	↔ desvenlafaxine expected	No dose adjustment needed
Duloxetine	BIC, CAB (PO and IM), DTG, RAL	↔ duloxetine expected	No dose adjustment needed
	EVG/c	↑ duloxetine possible	No dose adjustment needed
Mirtazapine	BIC, CAB (PO and IM), DTG, RAL	↔ mirtazapine expected	No dose adjustment needed
	EVG/c	↑ mirtazapine possible	Monitor for mirtazapine-related adverse events. Mirtazapine dose reduction may be necessary.
Nefazodone	BIC, CAB (PO and IM), DTG, RAL	↔ nefazodone expected	No dose adjustment needed
	EVG/c	↑ nefazodone expected	Consider alternative ARV or antidepressant.
Trazodone	BIC, CAB (PO and IM), DTG, RAL	↔ trazodone expected	No dose adjustment needed
	EVG/c	↑ trazodone possible	Titrate dose based on antidepressant response and monitor for trazodone-related adverse events.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Tricyclic Antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	BIC, CAB (PO and IM), DTG, RAL	↔ TCA expected	No dose adjustment needed
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA. Titrate dose carefully based on antidepressant response and/or drug concentrations.
Selective Serotonin Reuptake Inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine)	EVG/c	↔ sertraline	No dose adjustment needed
	EVG/c	↑ other SSRIs possible	Initiate with lowest dose of SSRI. Titrate dose carefully based on antidepressant response.
	BIC, CAB (PO and IM), DTG, RAL	↔ SSRI expected	No dose adjustment needed
Venlafaxine	BIC, CAB (PO and IM), DTG, RAL	↔ venlafaxine expected	No dose adjustment needed
	EVG/c	↑ venlafaxine possible	Monitor for venlafaxine-related adverse events.
Antipsychotics			
Aripiprazole	BIC, CAB (PO and IM), DTG, RAL	↔ aripiprazole expected	No dose adjustment needed
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate based on aripiprazole effectiveness and adverse events. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6-poor metabolizers or who have major depressive disorder.
Brexpiprazole	BIC, CAB (PO and IM), DTG, RAL	↔ brexpiprazole expected	No dose adjustment needed
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on brexpiprazole effectiveness and adverse events. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6-poor metabolizers or who have major depressive disorder.
Cariprazine	BIC, CAB (PO and IM), DTG, RAL	↔ cariprazine expected	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ cariprazine expected	**Starting Cariprazine in a Patient Who Is Already Receiving EVG/c** • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum of cariprazine 3 mg daily. If EVG/c is withdrawn, cariprazine dose may need to be increased. **Starting EVG/c in a Patient Who Is Already Receiving Cariprazine** • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce the dose by half. For patients receiving cariprazine 4.5 mg daily, reduce dose to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients receiving cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If EVG/c is withdrawn, cariprazine dose may need to be increased.
Iloperidone	BIC, CAB (PO and IM), DTG, RAL	↔ iloperidone expected	No dose adjustment needed
	EVG/c	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lumateperone	BIC, CAB (PO and IM), DTG, RAL	↔ lumateperone expected	No dose adjustment needed
	EVG/c	↑ lumateperone expected	**Do not coadminister.**
Lurasidone	BIC, CAB (PO and IM), DTG, RAL	↔ lurasidone expected	No dose adjustment needed
	EVG/c	↑ lurasidone expected	**Contraindicated**
Olanzapine, Olanzapine/ Samidorphan	All INSTIs	↔ olanzapine expected	No dose adjustment needed
	EVG/c	↔ olanzapine expected ↑ samidorphan possible	No dose adjustment needed
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., perphenazine, risperidone, thioridazine)	EVG/c	↑ antipsychotic possible	Initiate antipsychotic at a low dose. Antipsychotic dose reduction may be needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Pimavanserin	BIC, CAB (PO and IM), DTG, RAL	↔ pimavanserin expected	No dose adjustment needed
	EVG/c	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg.
Pimozide	BIC, CAB (PO and IM), DTG, RAL	↔ pimozide expected	No dose adjustment needed
	EVG/c	↑ pimozide expected	**Contraindicated**
Quetiapine	BIC, CAB (PO and IM), DTG, RAL	↔ quetiapine expected	No dose adjustment needed
	EVG/c	↑ quetiapine AUC expected	**Starting Quetiapine in a Patient Receiving EVG/c** • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse events. **Starting EVG/c in a Patient Receiving a Stable Dose of Quetiapine** • Reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine efficacy and adverse events.
Ziprasidone	BIC, CAB (PO and IM), DTG, RAL	↔ ziprasidone expected	No dose adjustment needed
	EVG/c	↑ ziprasidone possible	Monitor for ziprasidone-related adverse events.
Antimigraine			
Ergot Derivatives	BIC, CAB (PO and IM), DTG, RAL	↔ dihydroergotamine, ergotamine, and methylergonovine expected	No dose adjustment needed
	EVG/c	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated**
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists			
Atogepant	BIC, CAB (PO and IM), DTG, RAL	↔ atogepant expected ↑ atogepant expected	No dose adjustment needed
	EVG/c	↑ atogepant expected	Chronic migraine: **Do not coadminister.** Episodic migraine: Administer atogepant at a dose of 10 mg once daily.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rimegepant	BIC, CAB (PO and IM), DTG, RAL	↔ rimegepant expected	No dose adjustment needed
	EVG/c	↑ rimegepant expected	**Do not coadminister.**
Ubrogepant	BIC, CAB (PO and IM), DTG, RAL	↔ ubrogepant expected	No dose adjustment needed
	EVG/c	↑ ubrogepant expected	**Contraindicated**
Zavegepant	BIC, CAB (PO and IM), DTG, RAL	↔ zavegepant expected	No dose adjustment needed
	EVG/c	↑ zavegepant expected	**Do not coadminister.**
Serotonin 5-HT1B, 1D Receptor Agonist			
Almotriptan	BIC, CAB (PO and IM), DTG, RAL	↔ almotriptan expected	No dose adjustment needed
	EVG/c	↑ almotriptan expected	Administer single dose of almotriptan 6.25 mg. Maximum dose should not exceed 12.5 mg in a 24-hour period.
Eletriptan	BIC, CAB (PO and IM), DTG, RAL	↔ eletriptan expected	No dose adjustment needed
	EVG/c	↑ eletriptan expected	**Contraindicated**
Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan Zolmitriptan	All INSTIs	↔ triptan expected	No dose adjustment needed
Antifungals			
Ibrexafungerp	BIC, CAB (PO and IM), DTG, RAL	↔ ibrexafungerp expected	No dose adjustment needed
	EVG/c	↑ ibrexafungerp expected	Reduce ibrexafungerp dose to 150 mg twice daily.
Isavuconazole	BIC, CAB (PO and IM), DTG, RAL	↑ INSTI possible	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ isavuconazole expected ↑ or ↓ EVG and COBI possible	**Contraindicated**
Itraconazole	BIC	↑ BIC expected	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ itraconazole expected	No dose adjustment needed
	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole concentrations to guide dose adjustments. **Do not coadminister** with high itraconazole doses (>200 mg/day) unless guided by itraconazole concentrations.
Posaconazole	BIC	↑ BIC expected	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ posaconazole expected	No dose adjustment needed
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ voriconazole expected	No dose adjustment needed
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	**Do not coadminister** voriconazole and COBI, unless the benefit outweighs the risk. If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antimalarials			
Artemether/ Lumefantrine	BIC	↔ antimalarial expected	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ antimalarial expected	No dose adjustment needed
	EVG/c	↑ artemether and lumefantrine possible	Monitor for artemether and lumefantrine-related adverse events, including QTc prolongation.
Artesunate	All INSTIs	↔ dihydroartemisinin expected	No dose adjustment needed
Atovaquone/ Proguanil	All INSTIs	↔ atovaquone/proguanil expected	No dose adjustment needed
Mefloquine	CAB (PO and IM), DTG, RAL	↔ mefloquine expected	No dose adjustment needed
	EVG/c	↑ mefloquine possible	Monitor for mefloquine-related adverse events, including psychiatric symptoms and QTc prolongation.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Glucose-Lowering			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for adverse events of metformin.
	CAB (PO and IM), RAL	↔ metformin expected	No dose adjustment needed
	DTG	**DTG 50 mg Once Daily Plus Metformin 500 mg Twice Daily** • Metformin AUC ↑ 79% and C_{max} ↑ 66% **DTG 50 mg Twice Daily Plus Metformin 500 mg Twice Daily** • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at the lowest dose and titrate based on glycemic control. Monitor for adverse events of metformin. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse events of metformin.
	EVG/c	↑ metformin possible	No dose adjustment needed
Saxagliptin	BIC, CAB (PO and IM), DTG, RAL	↔ saxagliptin expected	No dose adjustment needed
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/ Saxagliptin	BIC, CAB (PO and IM), DTG, RAL	↔ dapagliflozin or saxagliptin expected	No dose adjustment needed
	EVG/c	↑ saxagliptin expected	**Do not coadminister.** Dapagliflozin is available only as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended.**
Antiplatelets			
Clopidogrel	BIC, CAB (PO and IM), DTG, RAL	↔ clopidogrel expected	No dose adjustment needed
	EVG/c	↓ clopidogrel active metabolite, with impaired platelet inhibition expected	**Do not coadminister.**
Prasugrel	BIC, CAB (PO and IM), DTG, RAL	↔ prasugrel expected	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↓ prasugrel active metabolite, with no impairment of platelet inhibition expected	No dose adjustment needed
Ticagrelor	BIC, CAB (PO and IM), DTG, RAL	↔ ticagrelor expected	No dose adjustment needed
	EVG/c	↑ ticagrelor expected	**Do not coadminister.**
Vorapaxar	BIC, CAB (PO and IM) DTG, RAL	↔ vorapaxar expected	No dose adjustment needed
	EVG/c	↑ vorapaxar expected	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis			
Atovaquone	All INSTIs	↔ atovaquone expected	No dose adjustment needed
Antivirals—Hepatitis C			
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment needed
	CAB (PO and IM)	↔ CAB, elbasvir, and grazoprevir expected	No dose adjustment needed
	DTG	↔ DTG ↔ elbasvir ↔ grazoprevir	No dose adjustment needed
	EVG/c	↑ elbasvir expected ↑ grazoprevir expected	**Do not coadminister.**
	RAL	↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir ↔ elbasvir ↔ grazoprevir	No dose adjustment needed
Glecaprevir/ Pibrentasvir	BIC, CAB (PO and IM)	↔ BIC or CAB expected	No dose adjustment needed
	DTG	↔ DTG and glecaprevir/ pibrentasvir	No dose adjustment needed
	RAL	No significant effect RAL AUC ↑ 47%	
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57%	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		EVG AUC ↑ 47%	If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
Ledipasvir/ Sofosbuvir	BIC, DTG, RAL	↔ BIC, DTG, and RAL	No dose adjustment needed
	CAB (PO and IM)	↔ CAB expected	No dose adjustment needed
	EVG/c/TDF/ FTC	↑ TDF expected ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/TAF/ FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment needed
Sofosbuvir	BIC, CAB (PO and IM), DTG, EVG/C	↔ INSTI expected ↔ sofosbuvir expected	No dose adjustment needed
	RAL	↔ RAL and sofosbuvir	No dose adjustment needed
Sofosbuvir/ Velpatasvir	BIC, DTG, RAL	↔ sofosbuvir and velpatasvir	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events.
	CAB (PO and IM)	↔ CAB expected ↔ sofosbuvir and velpatasvir expected	
	EVG/c	↔ EVG/c/TAF/FTC Velpatasvir AUC ↑ 50%	
Sofosbuvir/ Velpatasvir/ Voxilaprevir	BIC	**When Administered With Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/ 100 mg/100 mg) Plus Voxilaprevir 100 mg** • ↔ BIC, sofosbuvir, velpatasvir, voxilaprevir	No dose adjustment needed
	EVG/c	**When Administered With Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/ 100 mg/100 mg) Plus Voxilaprevir 100 mg** • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ sofosbuvir, velpatasvir, and voxilaprevir expected	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antivirals—Miscellaneous (e.g., for CMV, Mpox)			
Brincidofovir	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected	No dose adjustment needed
	EVG/c	↑ brincidofovir possible ↑ EVG possible	Administer EVG/c dose at least 3 hours after administering brincidofovir and monitor for brincidofovir-related adverse events, including elevations in ALT/AST and bilirubin and GI adverse events.
Cidofovir	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ INSTI expected ↔ cidofovir expected	No dose adjustment needed
Tecovirimat	CAB (IM)	↔ CAB expected	No dose adjustment needed Do not initiate CAB/RPV IM during or within 2 weeks after tecovirimat treatment. (Refer to Table 24b for interaction with RPV.)
	BIC, CAB (PO), DTG, EVG/c, RAL	↔ INSTI expected	No dose adjustment needed
Antivirals—SARS-CoV-2			
Molnupiravir	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ INSTI and molnupiravir expected	No dose adjustment needed
Ritonavir-boosted Nirmatrelvir	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI and ritonavir-boosted nirmatrelvir expected	No dose adjustment needed.
	EVG/c/FTC/TAF	↑ TAF possible ↔ ritonavir-boosted nirmatrelvir expected	No dose adjustment needed
Remdesivir	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ INSTI and remdesivir expected	No dose adjustment needed
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	All INSTIs	↔ arformoterol or formoterol expected	No dose adjustment needed
Indacaterol	BIC, CAB (PO and IM), DTG, RAL	↔ indacaterol expected	No dose adjustment needed
	EVG/c	↑ indacaterol expected	

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Olodaterol	BIC, CAB (PO and IM), DTG, RAL	↔ olodaterol expected	No dose adjustment needed
	EVG/c	↑ olodaterol expected	
Salmeterol	BIC, CAB (PO and IM), DTG, RAL	↔ salmeterol expected	No dose adjustment needed
	EVG/c	↑ salmeterol possible	**Do not coadminister** due to the potential for increased risk of salmeterol-associated cardiovascular events.
Cardiac Medications			
Antiarrhythmics			
Amiodarone	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ amiodarone expected	No dose adjustment needed
	EVG/c	↑ amiodarone expected	**Do not coadminister** unless the benefits outweigh the risks. If coadministration is necessary, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone concentrations.
Digoxin	BIC, CAB (PO and IM), RAL	↔ digoxin expected	No dose adjustment needed
	EVG/c	Digoxin C_{max} ↑ 41% and ↔ AUC	Therapeutic drug monitoring for digoxin is recommended if available.
Dofetilide	CAB (PO and IM)	↔ dofetilide expected	No dose adjustment needed
	BIC, DTG	↑ dofetilide expected	**Contraindicated**
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Disopyramide	BIC, CAB (PO and IM), RAL	↔ disopyramide expected	No dose adjustment needed
	DTG	↑ disopyramide possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor disopyramide concentrations and for antiarrhythmic-related adverse events.
	EVG/c	↑ disopyramide expected	**Do not coadminister.**
Dronedarone	BIC, CAB (PO and IM), DTG, RAL	↔ dronedarone expected	No dose adjustment needed
	EVG/c	↑ dronedarone expected	**Contraindicated**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Flecainide	BIC, CAB (PO and IM), DTG, RAL	↔ flecainide expected	No dose adjustment needed
	EVG/c	↑ flecainide possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor flecainide concentrations and for antiarrhythmic-related adverse events.
Propafenone	BIC, CAB (PO and IM), DTG, RAL	↔ propafenone expected	No dose adjustment needed
	EVG/c	↑ propafenone possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor propafenone concentrations and for antiarrhythmic-related adverse events.
Mexiletine	BIC, CAB (PO and IM), DTG, RAL	↔ mexiletine expected	No dose adjustment needed
	EVG/c	↑ mexiletine possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor mexiletine concentrations and for antiarrhythmic-related adverse events.
Systemic Lidocaine	BIC, CAB (PO and IM), DTG, RAL	↔ lidocaine expected	No dose adjustment needed
	EVG/c	↑ lidocaine possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor lidocaine concentrations and for antiarrhythmic-related adverse events.
Quinidine	BIC, CAB (PO and IM), DTG, RAL	↔ quinidine expected	No dose adjustment needed
	EVG/c	↑ quinidine possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor quinidine concentrations and for antiarrhythmic-related adverse events.
Beta-Blockers			
Atenolol, Bisoprolol, Carvedilol, Metoprolol, Nadolol, Nebivolol, Sotalol	CAB (PO and IM), RAL	↔ beta-blocker expected	No dose adjustment needed
	BIC, DTG, EVG/c	↑ beta-blocker possible	Beta-blocker dose may need to be decreased; adjust dose based on clinical response.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Calcium Channel Blockers			
Calcium Channel Blockers	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment needed
	CAB (PO and IM), DTG, RAL	↔ CCB expected	No dose adjustment needed
	EVG/c	↑ CCB possible	Titrate CCB dose and monitor for CCB efficacy and adverse events.
Cardiac—Other			
Bosentan	BIC, DTG	↓ BIC and DTG possible	No dose adjustment needed
	CAB (PO and IM)	↔ bosentan expected	Consider using alternative ARV or an alternative to bosentan because bosentan may ↓ RPV, which is co-packaged and coadministered with CAB IM. If bosentan is used with RPV, monitor virologic response to ART.
	RAL	↔ bosentan expected	No dose adjustment needed
	EVG/c	↑ bosentan possible	**In Patients on EVG/c ≥10 Days** • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. **In Patients on Bosentan Who Require EVG/c** • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Dofetilide	BIC, DTG	↑ dofetilide expected	**Contraindicated**
	CAB (PO and IM), RAL	↔ dofetilide expected	No dose adjustment needed
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Eplerenone	BIC, CAB (PO and IM), DTG, RAL	↔ eplerenone expected	No dose adjustment needed
	EVG/c	↑ eplerenone expected	**Contraindicated**
Ivabradine	BIC, CAB (PO and IM), DTG, RAL	↔ ivabradine expected	No dose adjustment needed
	EVG/c	↑ ivabradine expected	**Contraindicated**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Mavacamten	BIC, CAB (PO and IM), DTG, RAL	↔ mavacamten expected	No dose adjustment needed
	EVG/c	↑ mavacamten expected	**Contraindicated**
Ranolazine	BIC, CAB (PO and IM), DTG, RAL	↔ ranolazine expected	No dose adjustment needed
	EVG/c	↑ ranolazine expected	**Contraindicated**
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ glucocorticoid expected	No dose adjustment needed
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, CAB (PO and IM), DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed
	EVG/c	↑ glucocorticoid possible	**Do not coadminister** unless the potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider using an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ glucocorticoid expected	No dose adjustment needed
	EVG/c	↑ glucocorticoid possible ↓ EVG possible	**Do not coadminister** unless the potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	BIC	↓ BIC possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected	No dose adjustment needed
	EVG/c	↓ EVG and COBI possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, CAB (PO and IM), DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministration is necessary, monitor for adrenal insufficiency and Cushing's syndrome.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, CAB (PO and IM), DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed
	EVG/c	↑ glucocorticoid expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Herbal Products			
St. John's Wort	BIC, CAB (PO and IM), DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI expected	**Contraindicated**
Hormonal Therapies			
Injectable Contraceptives Depot MPA	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI and injectable contraceptive expected	No dose adjustment needed
	EVG/c	↑ MPA possible	No dose adjustment needed
Oral Contraceptives (e.g., desogestrel, drospirenone, ethinyl estradiol, levonorgestrel, norethindrone, norgestimate)	BIC, CAB (PO, IM), DTG, RAL	↔ ethinyl estradiol and norgestimate with DTG ↔ ethinyl estradiol and levonorgestrel with CAB PO ↔ ethinyl estradiol and norgestimate expected with BIC, RAL ↔ norgestimate expected with CAB PO and IM ↔ levonorgestrel expected ↔ drospirenone expected ↔ norethindrone expected	No dose adjustment needed
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ > 2-fold Ethinyl estradiol AUC ↓ 25% and C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and may include insulin resistance, dyslipidemia, acne, and venous thrombosis. Decreased ethinyl estradiol may lead to more intermenstrual bleeding. Weigh the risks and benefits of using the drug and consider using an alternative ARV or contraceptive method.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		↑ drospirenone possible	Clinical monitoring is recommended due to the potential for hyperkalemia. Consider using alternative ARV or contraceptive method.
		↑ levonorgestrel possible ↑ norethindrone expected	No dose adjustment needed
Subdermal Implant Contraceptives (e.g., etonogestrel, levonorgestrel)	BIC, CAB (PO and IM), DTG, RAL	Etonogestrel ↑ 27% with DTG ↔ etonogestrel or levonorgestrel expected with BIC, CAB, RAL	No dose adjustment needed
	EVG/c	↑ etonogestrel expected ↑ levonorgestrel expected	No dose adjustment needed
Transdermal Contraceptives (e.g., ethinyl estradiol/ norelgestromin, ethinyl estradiol/ levonorgestrel)	BIC, CAB (PO, IM), DTG, RAL	↔ contraceptive expected	No dose adjustment needed
	EVG/c	↑ progestin possible ↓ ethinyl estradiol possible	No dose adjustment needed
Vaginal Ring Contraceptives (e.g., etonogestrel/ ethinyl estradiol, segesterone/ethinyl estradiol)	BIC, CAB (PO, IM), DTG, RAL	↔ contraceptive expected	No dose adjustment needed
	EVG/c	↑ progestin possible ↓ ethinyl estradiol possible	For segesterone/ethinyl estradiol vaginal rings, use alternative ARV or contraceptive methods.
Emergency Contraceptives Levonorgestrel (PO)	BIC, CAB (PO, IM), DTG, RAL	↔ levonorgestrel expected	No dose adjustment needed
	EVG/c	↑ levonorgestrel possible	No dose adjustment needed
Hormonal Therapies—Gender-Affirming and Menopause			
Gender-Affirming Therapy	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed
	BIC, CAB (PO and IM), DTG, RAL	↔ estrogen expected	No dose adjustment needed
		↔ testosterone expected	No dose adjustment needed
	EVG/c	↑ or ↓ estradiol possible ↑ cyproterone, dutasteride, and finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations.
		↑ testosterone possible	Monitor masculinizing effects of testosterone and monitor for adverse effects. Adjust testosterone dose as necessary.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Menopausal Replacement Therapy	BIC, CAB (PO and IM), DTG, RAL	↔ estrogen expected with estradiol or conjugated estrogen (equine and synthetic) ↔ drospirenone, MPA, and micronized progesterone expected	No dose adjustment needed
	EVG/c	↓ or ↑ estrogen possible ↑ drospirenone possible ↑ oral MPA possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, CAB (PO and IM), DTG, RAL	↔ immunosuppressant expected	No dose adjustment needed
	EVG/c	↑ immunosuppressant possible	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant. Monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Lipid-Modifying			
Atorvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ atorvastatin expected	No dose adjustment needed
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Administer the lowest effective dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
Fluvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ fluvastatin expected	No dose adjustment needed
	EVG/c	↑ fluvastatin possible	Administer the lowest effective fluvastatin dose while monitoring for adverse events.
Lomitapide	BIC, CAB (PO and IM), DTG, RAL	↔ lomitapide expected	No dose adjustment needed
	EVG/c	↑ lomitapide expected	**Contraindicated**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lovastatin	BIC, CAB (PO and IM), DTG, RAL	↔ lovastatin expected	No dose adjustment needed
	EVG/c	Significant ↑ lovastatin expected	**Contraindicated**
Pitavastatin, Pravastatin	BIC, CAB (PO and IM), DTG, RAL	↔ statin expected	No dose adjustment needed
	EVG/c	No data	No dose adjustment needed. Monitor for adverse events.
Rosuvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ rosuvastatin expected	No dose adjustment needed
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Administer the lowest effective dose while monitoring for adverse events.
Simvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ simvastatin expected	No dose adjustment needed
	EVG/c	Significant ↑ simvastatin expected	**Contraindicated**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	BIC, CAB (PO and IM), DTG	↔ buprenorphine and norbuprenorphine (active metabolite) expected	No dose adjustment needed
	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 42% and C_{min} ↑ 57%	No dose adjustment needed. Monitor for adverse events of buprenorphine. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ buprenorphine and norbuprenorphine (active metabolite) (sublingual) ↔ buprenorphine or norbuprenorphine (active metabolite) expected (implant)	No dose adjustment needed
Fentanyl	BIC, CAB (PO and IM), DTG, RAL	↔ fentanyl expected	No dose adjustment needed
	EVG/c	↑ fentanyl	Monitor for fentanyl efficacy and adverse events, including potentially fatal respiratory depression.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lofexidine	BIC, CAB (PO and IM), DTG, RAL	↔ lofexidine expected	No dose adjustment needed
	EVG/c	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	All INSTIs	↔ methadone	No dose adjustment needed
Tramadol	BIC, CAB (PO and IM), DTG, RAL	↔ tramadol and M1 (active metabolite) expected	No dose adjustment needed
	EVG/c	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.
PDE5 Inhibitors			
Avanafil	BIC, CAB (PO and IM), DTG, RAL	↔ avanafil expected	No dose adjustment needed
	EVG/c	No data	**Do not coadminister.**
Sildenafil	BIC, CAB (PO and IM), DTG, RAL	↔ sildenafil expected	No dose adjustment needed
	EVG/c	↑ sildenafil expected	**For Treatment of Erectile Dysfunction** • Start with sildenafil 25 mg every 48 hours and monitor for sildenafil-related adverse events. **Contraindicated** for treatment of PAH.
Tadalafil	BIC, CAB (PO and IM), DTG, RAL	↔ tadalafil expected	No dose adjustment needed
	EVG/c	↑ tadalafil expected	**For Treatment of Erectile Dysfunction** • Start with tadalafil 5 mg. Do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for tadalafil-related adverse events. **For Treatment of PAH** *In Patients on EVG/c >7 Days* • Start with tadalafil 20 mg once daily. Increase to tadalafil 40 mg once daily based on tolerability.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
			In Patients on Tadalafil who Require EVG/c • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, CAB (PO and IM), DTG, RAL	↔ vardenafil expected	No dose adjustment needed
	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for vardenafil-related adverse events.
Sedative/Hypnotics			
Benzodiazepines			
Alprazolam, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	BIC, CAB (PO and IM), DTG, RAL	↔ benzodiazepine expected	No dose adjustment needed
	EVG/c	↑ benzodiazepine possible	Dose reduction of benzodiazepine may be necessary. Initiate with a low dose and monitor for benzodiazepine-related adverse events. Consider using an alternative benzodiazepine, such as lorazepam, oxazepam, or temazepam.
Midazolam, Triazolam	BIC, CAB (PO and IM), RAL	↔ benzodiazepine expected	No dose adjustment needed
	DTG	**With DTG 25 mg** • ↔ midazolam AUC	No dose adjustment needed
	EVG/c	↑ midazolam expected ↑ triazolam expected	**Contraindicated** **Do not coadminister** triazolam or oral midazolam and EVG/c. Parenteral midazolam can be administered in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.
Orexin Receptor Antagonists			
Daridorexant, Lemborexant, Suvorexant	BIC, CAB (PO and IM), DTG, RAL	↔ daridorexant, lemborexant, suvorexant expected	No dose adjustment needed
	EVG/c	↑ daridorexant, lemborexant, suvorexant expected	**Do not coadminister.**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Other Sedatives			
Eszopiclone	BIC, CAB (PO and IM), DTG, RAL	↔ eszopiclone expected	No dose adjustment needed
	EVG/c	↑ eszopiclone expected	Start with lowest dose and increase to a max of 2 mg daily. Monitor for eszopiclone-related adverse events.
Zolpidem	BIC, CAB (PO and IM), DTG, RAL	↔ zolpidem expected	No dose adjustment needed
	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction of zolpidem may be necessary.
Miscellaneous Drugs			
Calcifediol	BIC, CAB (PO and IM), DTG, RAL	↔ calcifediol expected	No dose adjustment needed
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required. Monitor serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations.
Cisapride	BIC, CAB (PO and IM), DTG, RAL	↔ cisapride expected	No dose adjustment needed
	EVG/c	↑ cisapride expected	**Contraindicated**
Colchicine	BIC, CAB (PO and IM), DTG, RAL	↔ colchicine expected	No dose adjustment needed
	EVG/c	↑ colchicine expected	**Do not coadminister** in patients with hepatic or renal impairment. **For Treatment of Gout Flares** • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. **For Prophylaxis of Gout Flares** • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
			For Treatment of Familial Mediterranean Fever • Do not exceed colchicine 0.6 mg once daily or 0.3 mg twice daily.
Dronabinol	BIC, CAB (PO and IM), DTG, RAL	↔ dronabinol expected	No dose adjustment needed
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse events.
Eluxadoline	BIC, CAB (PO and IM), DTG, RAL	↔ eluxadoline expected	No dose adjustment needed
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse events.
Ergot Derivatives	BIC, CAB (PO and IM), DTG, RAL	↔ dihydroergotamine, ergotamine, and methylergonovine expected	No dose adjustment needed
	EVG/c	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated**
Finerenone	BIC, CAB (PO and IM), DTG, RAL	↔ finerenone expected	No dose adjustment needed
	EVG/c	↑ finerenone expected	**Contraindicated**
Flibanserin	BIC, CAB (PO and IM), DTG, RAL	↔ flibanserin expected	No dose adjustment needed
	EVG/c	↑ flibanserin expected	**Contraindicated**
Naloxegol	BIC, CAB (PO and IM), DTG, RAL	↔ naloxegol expected	No dosage adjustment needed
	EVG/c	↑ naloxegol expected	**Contraindicated**

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals. **Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids.	BIC	↔ BIC AUC if administered simultaneously with Fe or Ca and food BIC AUC ↓ 33% if administered simultaneously with $CaCO_3$ under fasting conditions BIC AUC ↓ 63% if administered simultaneously with Fe under fasting conditions	**With Supplements That Contain Ca or Fe** • Administer BIC and supplements that contain Ca or Fe together with food. **Do not coadminister** BIC under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.
	CAB	↓ INSTI possible	If coadministration is necessary, administer INSTI at least 2 hours before or at least 4 hours after supplements that contain polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic response. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
	DTG	DTG AUC ↓ 39% if administered simultaneously with $CaCO_3$ under fasting conditions DTG AUC ↓ 54% if administered simultaneously with Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	**With Supplements That Contain Ca or Fe** • Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hours before or at least 6 hours after supplement. **Do not coadminister** DTG under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.
	EVG/c, RAL	↓ INSTI possible	If coadministration is necessary, administer INSTI at least 2 hours before or at least 6 hours after supplements that contain polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic response. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Praziquantel	BIC, CAB (PO and IM), DTG, RAL	↔ praziquantel and INSTI expected	No dose adjustment needed
	EVG/c	↑ praziquantel possible	Consider alternative ARV. If coadministration is necessary, monitor for praziquantel-related adverse events.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: Al = aluminum; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; AUC = area under the curve; BIC = bictegravir; Ca = calcium; CAB = cabotegravir; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CMV = cytomegalovirus; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P450; DTG = dolutegravir; DVT = deep vein thrombosis; ECG = electrocardiogram; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; GI = gastrointestinal; IM = intramuscular; INR = international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; MPA = medroxyprogesterone acetate; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PE = pulmonary embolism; PO = orally; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; Zn = zinc

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Updated: September 12, 2024
Reviewed: September 12, 2024

In the table below, "no dose adjustment needed" indicates that the U.S. Food and Drug Administration–approved dose of maraviroc (MVC) 300 mg twice daily should be used. Recommendations for managing a particular drug interaction may differ, depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication.

Concomitant Drug Class/ Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials—Macrolides		
Azithromycin	↔ MVC expected	No dose adjustment needed
Clarithromycin	↑ MVC possible	MVC 150 mg twice daily
Erythromycin	↑ MVC possible	No dose adjustment needed
Antifungals		
Fluconazole	↑ MVC possible	No dose adjustment needed
Isavuconazole	↑ MVC possible	No dose adjustment needed
Itraconazole	↑ MVC possible	MVC 150 mg twice daily
Posaconazole	↑ MVC possible	MVC 150 mg twice daily
Voriconazole	↑ MVC possible	MVC 150 mg twice daily
Antimycobacterials		
Rifabutin	MVC AUC ↔ and C_{min} ↓ 30%	**If Used *Without* a Strong CYP3A Inhibitor** • MVC 300 mg twice daily **If Used *With* a Strong CYP3A Inhibitor** • MVC 150 mg twice daily
Rifampin	MVC AUC ↓ 63%	**If Used *Without* a Strong CYP3A Inhibitor** • MVC 600 mg twice daily **If Used *With* a Strong CYP3A Inhibitor** • Consider alternative ARV or antimycobacterial
Rifapentine	**Rifapentine Weekly and Daily** ↓ MVC expected	Do not coadminister.

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiseizure		
Carbamazepine, Phenobarbital, Phenytoin	↓ MVC possible	**If Used *Without* a Strong CYP3A Inhibitor** • MVC 600 mg twice daily **If Used *With* a Strong CYP3A Inhibitor** • MVC 150 mg twice daily
Eslicarbazepine	↓ MVC possible	Consider alternative ARV or anticonvulsant.
Oxcarbazepine	↓ MVC possible	Consider alternative ARV or anticonvulsant.
Antivirals—Hepatitis C Direct-Acting Antivirals		
Elbasvir/Grazoprevir	↔ MVC expected	No dose adjustment needed
Ledipasvir/Sofosbuvir	↔ MVC expected	No dose adjustment needed
Glecaprevir/Pibrentasvir	↔ MVC expected	No dose adjustment needed
Simeprevir	↔ MVC expected	No dose adjustment needed
Sofosbuvir	↔ MVC expected	No dose adjustment needed
Sofosbuvir/Velpatasvir	↔ MVC expected	No dose adjustment needed
Sofosbuvir/Velpatasvir/Voxilaprevir	↔ MVC expected	No dose adjustment needed
Antivirals—Miscellaneous (e.g., for CMV, Mpox)		
Brincidofovir	↔ MVC expected	No dose adjustment needed
Cidofovir	↔ MVC expected	No dose adjustment needed
Tecovirimat	**When Given With MVC Without a Boosted PI or Other Potent CYP3A4 Inhibitors** • ↓ MVC possible but not expected to be clinically relevant **When Given With MVC Plus a Boosted PI or Other Potent CYP3A4 Inhibitors** • ↑ MVC expected	**If Used *Without* a Strong CYP3A Inhibitor** • No dose adjustment needed **If Used *With* a Strong CYP3A Inhibitor** • MVC 150 mg twice daily
Antivirals—SARS-CoV-2		
Molnupiravir	↔ MVC expected	No dose adjustment needed
Remdesivir	↔ MVC expected	No dose adjustment needed
Ritonavir-Boosted Nirmatrelvir	**MVC With Ritonavir 100 mg Twice Daily** • MVC AUC ↑ 161%	MVC 150 mg twice daily
Herbal Products		
St. John's Wort	↓ MVC expected	Do not coadminister.

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies		
Hormonal Contraceptives	↔ ethinyl estradiol or levonorgestrel	No dose adjustment needed
Gender-Affirming Hormone Therapies	↔ MVC or gender-affirming hormones expected	No dose adjustment needed
Menopausal Hormone Replacement Therapy	↔ MVC or hormone replacement therapies expected	No dose adjustment needed
Antiretroviral Drugs		
Attachment Inhibitor		
FTR[a]	MVC AUC ↑ 25% ↔ TMR[a]	No dose adjustment needed
Capsid Inhibitor		
LEN (SQ and PO)	↑ MVC possible	No dose adjustment needed
INSTIs		
BIC, CAB (IM and PO), DTG	↔ MVC expected	No dose adjustment needed
EVG/c	↑ MVC possible	MVC 150 mg twice daily.
RAL	MVC AUC ↓ 21% RAL AUC ↓ 37%	No dose adjustment needed
NNRTIs		
DOR, RPV (IM and PO)	↔ MVC expected	No dose adjustment needed
EFV	MVC AUC ↓ 45%	**If Used *Without* a Strong CYP3A Inhibitor** • MVC 600 mg twice daily **If Used *With* a Strong CYP3A Inhibitor** • MVC 150 mg twice daily
ETR	MVC AUC ↓ 53%	**If Used *Without* a Strong CYP3A Inhibitor** • MVC 600 mg twice daily **If Used *With* a Strong CYP3A Inhibitor** • MVC 150 mg twice daily
PIs		
ATV/c, ATV/r	**With (ATV/r 300 mg/100 mg) Once Daily** • MVC AUC ↑ 388%	MVC 150 mg twice daily.

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
DRV/c, DRV/r	**With (DRV/r 600 mg/100 mg) Twice Daily** • MVC AUC ↑ 305% **With (DRV/r 600 mg/100 mg) Twice Daily and ETR** • MVC AUC ↑ 210%	MVC 150 mg twice daily

[a] FTR is a prodrug metabolized to its active moiety, TMR. Therefore, the effect on gp120-directed attachment inhibitor in the table refers to TMR concentrations.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; CAB = cabotegravir; C_{min} = minimum plasma concentration; CMV = cytomegalovirus; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; ; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; TMR = temsavir

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Updated: September 12, 2024
Reviewed: September 12, 2024

Fostemsavir (FTR), an HIV-1 gp120-directed attachment inhibitor, is a prodrug of temsavir (TMR). In this table, the effect on gp120-directed attachment inhibitor refers to TMR concentrations. Recommendations for managing a particular drug interaction may differ depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. Providers should exercise their clinical judgment to select the most appropriate alternative medication to use in cases where an interacting drug needs to be replaced with an alternative.

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers		
H2 Receptor Antagonists	↔ TMR	No dose adjustment needed
Anticonvulsants		
Carbamazepine, Phenobarbital, Phenytoin	↓ TMR expected	**Contraindicated**
Antibacterials—Antimycobacterials		
Rifabutin	**With Rifabutin 300 mg Once Daily and Without RTV** • TMR AUC ↓ 30% **With Rifabutin 150 mg Once Daily and With RTV 100 mg Once Daily** • TMR AUC ↑ 66%	**If Used *Without* PI/r** • No dose adjustment needed **If Used *With* PI/r** • Recommended dose is rifabutin 150 mg once daily. • No dose adjustment of FTR
Rifampin	TMR AUC ↓ 82%	**Contraindicated**
Rifapentine	**Daily and Weekly Dosing** ↓ TMR expected	**Do not coadminister.**

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antivirals—Hepatitis C Direct-Acting Antivirals		
Elbasvir/Grazoprevir	↑ grazoprevir expected	Increased grazoprevir exposures may increase the risk of ALT elevations. **Use an alternative** HCV regimen.
Ledipasvir/Sofosbuvir	↔ expected	No dose adjustment needed
Glecaprevir/Pibrentasvir	↔ expected	No dose adjustment needed
Sofosbuvir	↔ expected	No dose adjustment needed
Sofosbuvir/Velpatasvir	↔ expected	No dose adjustment needed
Sofosbuvir/Velpatasvir/Voxilaprevir	↑ voxilaprevir expected	**Use an alternative** HCV regimen if possible.
Antivirals—Miscellaneous (e.g., for CMV, Mpox)		
Brincidofovir	↑ brincidofovir possible	Give FTR dose at least 3 hours after administering brincidofovir, and monitor for brincidofovir-related adverse events (i.e., elevations in ALT/AST and bilirubin and GI adverse events).
Cidofovir	↔ TMR expected	No dose adjustment needed
Tecovirimat	↔ TMR expected	No dose adjustment needed
Antivirals—SARS-CoV-2		
Molnupiravir	↔ expected	No dose adjustment needed
Ritonavir-Boosted Nirmatrelvir	TMR AUC ↑ 45%	No dose adjustment needed
Remdesivir	↔ expected	No dose adjustment needed
Herbal Products		
St. John's Wort	↓ TMR expected	**Contraindicated**
Hormonal Therapies		
Hormonal Contraceptives	Ethinyl estradiol AUC ↑ 40% ↔ norethindrone	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[a] or use alternative ARV or contraceptive methods.

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Gender-Affirming Hormone Therapies (e.g., estradiol, 5-alpha reductase inhibitors, testosterone)	↑ estradiol possible	Use lowest effective dose for estrogen-containing regimens.
Menopausal Hormone Replacement Therapy (e.g., conjugated estrogens, drospirenone, estradiol, medroxyprogesterone, progesterone)	↑ estrogens, estradiol possible	Use lowest effective dose for estrogen-containing regimens.
Lipid-Modifying Agents		
Atorvastatin, Fluvastatin, Pitavastatin, Simvastatin	↑ statin possible ↔ expected	Increased statin concentration may not be clinically relevant. Follow clinical guidelines. Administer the lowest effective statin dose while monitoring for adverse events.
Rosuvastatin	Rosuvastatin AUC ↑ 69%	Increased rosuvastatin concentration may not be clinically relevant. Follow clinical guidelines. Administer the lowest effective dose while monitoring for adverse events.
Narcotics and Treatment for Opioid Dependence		
Buprenorphine/Naloxone	Buprenorphine AUC ↑ 30% Norbuprenorphine (active metabolite) AUC ↑ 39%	No dose adjustment needed
Methadone	↔ Total methadone ↔ R(−) methadone (active metabolite) ↔ S(+) methadone	No dose adjustment needed
Antiretroviral Drugs		
Capsid Inhibitor		
LEN (SQ and PO)	↔ TMR expected ↔ LEN expected	No dose adjustment needed

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
CCR5 Antagonist		
MVC	↔ TMR MVC AUC ↑ 25%	No dose adjustment needed
CD4 Post-Attachment Inhibitor		
IBA	↔ expected	No dose adjustment needed
INSTIs		
BIC, CAB (IM and PO), DTG, EVG/c	↔ TMR expected	No dose adjustment needed
RAL plus TDF	↔ TMR	No dose adjustment needed
NRTIs		
TDF	↔ TMR ↔ TDF	No dose adjustment needed
NNRTIs		
DOR, RPV (IM and PO)	↔ TMR expected	No dose adjustment needed
EFV	↓ TMR possible ↔ EFV expected	No dose adjustment needed
ETR	TMR AUC ↓ 50% ↔ ETR	No dose adjustment needed
ETR plus DRV/r	TMR C_{max} and AUC ↑ 34% to 53% ↔ DRV, RTV ETR AUC ↑ 28%	No dose adjustment needed
PIs		
ATV/c	↑ TMR expected ↔ ATV expected	No dose adjustment needed

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
ATV/r	TMR C_{max} and AUC ↑ 54% to 58% ↔ ATV, RTV	No dose adjustment needed
DRV/c	TMR C_{max} and AUC ↑ 79% to 97% ↔ DRV, RTV expected	No dose adjustment needed
DRV/r	TMR C_{max} and AUC ↑ 52% to 63% ↔ DRV, RTV	No dose adjustment needed

[a] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations also may be available.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; C_{max} = maximum plasma concentration; CAB = cabotegravir; CCR5 = C-C chemokine receptor type 5; CMV = cytomegalovirus; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; GI = gastrointestinal; gp120 = glycoprotein 120; HCV = hepatitis C virus; IBA = ibalizumab; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted PI; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; TDF = tenofovir disoproxil fumarate; TMR = temsavir

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Updated: September 12, 2024
Reviewed: September 12, 2024

This table provides information on the known or predicted interactions between lenacapavir (LEN), an HIV capsid inhibitor, and other drugs, including antiretroviral (ARV) drugs.

LEN is available as an oral tablet (to be used only as initial therapy) and a long-acting injectable formulation that is administered every 6 months. LEN is a moderate cytochrome P450 (CYP) 3A4 inhibitor and may increase the concentration of drugs metabolized by CYP3A4. Due to the long half-life of the injectable formulation, this inhibitory effect may persist, and clinicians should continue to assess for drug interactions for up to 9 months after the last LEN injection. Recommendations for managing a particular drug interaction may differ depending on whether LEN is being initiated in a patient on a stable concomitant medication or whether a new medication is being initiated in a patient on a stable LEN-containing ARV regimen.

The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. Providers should exercise their clinical judgment to select the most appropriate alternative medication to use in cases where an interacting drug needs to be replaced with an alternative. People with HIV should be counseled about the importance of informing all their health care providers about their HIV regimen prior to starting any new concomitant medications (e.g., prescription, over-the-counter, and herbal or dietary supplements) to minimize the risk of drug–drug interactions.

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers		
Antacids, H2 Receptor Antagonists, Proton Pump Inhibitors	↔ expected	No dose adjustment needed
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia		
Alfuzosin	↑ alfuzosin expected	Consider an alternative to alfuzosin or an alternative ARV. If coadministered, monitor blood pressure.
Doxazosin	↑ doxazosin possible	No dose adjustment needed. Monitor blood pressure.
Tamsulosin	↑ tamsulosin possible	Initiate tamsulosin at 0.4 mg/day. Monitor blood pressure.
Terazosin	↔ expected	No dose adjustment needed
Silodosin	↑ silodosin possible	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials—Antimycobacterials		
Bedaquiline	↑ bedaquiline expected	Consider alternatives unless benefits outweigh risks. Monitor liver function and ECG for QTc prolongation.
Rifabutin	↓ LEN expected	**Do not coadminister.**
Rifampin	LEN AUC ↓ 84%	**Contraindicated**
Rifapentine	**Daily and Weekly Dosing** • ↓ LEN expected	**Do not coadminister.**
Antibacterials—Macrolides		
Azithromycin	↔ expected	No dose adjustment needed
Clarithromycin	↑ LEN possible	No dose adjustment needed
Erythromycin	↑ LEN possible	No dose adjustment needed
Anticoagulants		
Apixaban	↑ apixaban possible	No dose adjustment needed Monitor for apixaban-related adverse events, such as increased bleeding.
Dabigatran	↑ dabigatran possible	No dose adjustment needed Monitor for dabigatran-related adverse events, such as increased bleeding.
Edoxaban	↑ edoxaban possible	No dose adjustment needed Monitor for edoxaban-related adverse events, such as increased bleeding.
Rivaroxaban	↑ rivaroxaban possible	Monitor for rivaroxaban-related adverse events, such as increased bleeding, and adjust rivaroxaban dose accordingly.
Warfarin	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below.		
Bupropion	↔ expected	No dose adjustment needed
Buspirone	↑ buspirone expected	Administer lowest dose of buspirone with caution and titrate buspirone dose based on clinical response. Dose reduction may be necessary. Monitor for buspirone-related adverse events.
Desvenlafaxine	↔ expected	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Duloxetine	↔ expected	No dose adjustment needed
Mirtazapine	↑ mirtazapine possible	No dose adjustment needed. Monitor for mirtazapine-related adverse events.
Nefazodone	↑ LEN possible	No dose adjustment needed
Selective Serotonin Reuptake Inhibitor (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine)	↑ paroxetine possible ↔ citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, vortioxetine expected	Dose reduction may be necessary with paroxetine. No dose adjustment needed
Trazodone	↑ trazodone expected	Administer lowest dose of trazodone and monitor for CNS and CV adverse events.
Tricyclic Antidepressants (e.g., amitriptyline, doxepin, nortriptyline)	↔ expected	No dose adjustment needed
Venlafaxine	↔ expected	No dose adjustment needed
Antipsychotics		
Aripiprazole	↑ aripiprazole possible	No dose adjustment needed
Brexpiprazole	↑ brexpiprazole expected	If patient is a known CYP2D6 poor metabolizer, then administer one-quarter of usual brexpiprazole dose.
Cariprazine	↑ cariprazine possible	No dose adjustment needed
Iloperidone	↑ iloperidone possible	No dose adjustment needed or consider dose reduction. Monitor for iloperidone-related adverse events.
Lumateperone	↑ lumateperone expected	Reduce dose of lumateperone to 21 mg once daily.
Lurasidone	↑ lurasidone expected	If LEN is added to lurasidone therapy, administer half of lurasidone dose. If lurasidone is added to LEN therapy, the recommended starting dose of lurasidone is 20 mg daily, and the maximum recommended dose is 80 mg daily.
Olanzapine **Olanzapine/Samidorphan**	↔ LEN olanzapine expected ↑ samidorphan possible	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Other Antipsychotics (e.g., clozapine, risperidone, thioridazine)	↑ clozapine possible	No dose adjustment needed. Monitor for clozapine-related adverse events.
	↑ risperidone possible	No dose adjustment needed
	↑ thioridazine possible ↓ LEN possible	**Do not coadminister.**
Pimavanserin	↑ pimavanserin possible	No dose adjustment needed. Monitor ECG for QTc prolongation.
Pimozide	↑ pimozide expected	**Contraindicated**
Quetiapine	↑ quetiapine expected	Consider alternatives unless benefits outweigh risks. Monitor ECG for QTc prolongation and consider dose reduction accordingly.
Ziprasidone	↔ expected	No dose adjustment needed
Antimigraine		
Ergot Derivatives	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Do not coadminister.**
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists		
Atogepant	↑ atogepant expected	No dose adjustment needed
Rimegepant	↑ rimegepant expected	Avoid a second dose of rimegepant within 48 hours.
Ubrogepant	↑ ubrogepant expected	Avoid a second dose of ubrogepant within 24 hours.
Zavegepant	↔ expected	No dose adjustment needed
Serotonin 5-HT1B, 1D Receptor Agonist		
Almotriptan	↔ expected	No dose adjustment needed
Eletriptan	↑ eletriptan expected	No dose adjustment needed. Monitor for eletriptan-related adverse events.
Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan Zolmitriptan	↔ expected	No dose adjustment needed
Antifungals		
Fluconazole	↑ LEN possible	No dose adjustment needed
Ibrexafungerp	↑ ibrexafungerp possible	No dose adjustment needed
Isavuconazole	↔ expected	No dose adjustment needed
Itraconazole	↑ LEN possible	No dose adjustment needed
Posaconazole	↑ LEN possible	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Voriconazole	↑ LEN AUC 41%	No dose adjustment needed
Antimalarials		
Artemether/Lumefantrine	↑ artemether and lumefantrine possible	Monitor for lumefantrine-related adverse events, including QTc prolongation.
Artesunate	↔ expected	No dose adjustment needed
Atovaquone/Proguanil	↔ expected	No dose adjustment needed
Mefloquine	↑ mefloquine possible	Monitor for mefloquine-related adverse events, including QTc prolongation.
Antiplatelets		
Clopidogrel	↓ clopidogrel active metabolite possible	Consider alternative ARV or antiplatelet drug. If coadministered, monitor for clopidogrel-related adverse events.
Prasugrel	↔ expected	No dose adjustment needed
Ticagrelor	↑ ticagrelor possible	No dose adjustment needed. Monitor for ticagrelor-related adverse events.
Vorapaxar	↑ vorapaxar possible	No dose adjustment needed
Antipneumocystis and Antitoxoplasmosis		
Atovaquone Oral suspension	↔ expected	No dose adjustment needed
Antiseizure		
Carbamazepine	↓ LEN expected	**Contraindicated**
Eslicarbazepine	↓ LEN expected	**Do not coadminister.**
Ethosuximide	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events and adjust ethosuximide dose accordingly.
Lamotrigine	↔ expected	No dose adjustment needed
Oxcarbazepine	↓ LEN expected	**Do not coadminister.**
Phenobarbital	↓ LEN expected	**Do not coadminister.**
Phenytoin	↓ LEN expected	**Contraindicated**
Primidone	↓ LEN expected	**Do not coadminister.**
Valproic Acid	↔ expected	No dose adjustment needed
Antivirals—Hepatitis C		
Elbasvir/Grazoprevir	↔ expected	No dose adjustment needed
Glecaprevir/Pibrentasvir	↔ expected	No dose adjustment needed
Ledipasvir/Sofosbuvir	↔ expected	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sofosbuvir/Velpatasvir	↔ expected	No dose adjustment needed
Sofosbuvir/Velpatasvir/Voxilaprevir	↔ expected	No dose adjustment needed
Antivirals—Miscellaneous (e.g., for CMV, Mpox)		
Brincidofovir	↔ expected	No dose adjustment needed
Cidofovir	↔ expected	No dose adjustment needed
Maribavir	↔ expected	No dose adjustment needed
Tecovirimat	↓ LEN possible	No dose adjustment needed
Valganciclovir	↔ expected	No dose adjustment needed
Antivirals—SARS-CoV-2		
Molnupiravir	↔ expected	No dose adjustment needed
Ritonavir-Boosted Nirmatrelvir	↑ LEN possible	No dose adjustment needed
Remdesivir	↔ expected	No dose adjustment needed
Antiretroviral Drugs		
CCR5 Antagonist		
MVC	↔ expected	No dose adjustment needed
CD4 Post-attachment Inhibitor		
IBA	↔ expected	No dose adjustment needed
gp120 Attachment Inhibitor		
FTR	↔ expected	No dose adjustment needed
INSTIs		
BIC, CAB (IM or PO), DTG, EVG/c, RAL	↔ expected	No dose adjustment needed
NRTIs		
ABC, 3TC, FTC	↔ expected	No dose adjustment needed
TAF	TAF AUC ↑ 32%	No dose adjustment needed
TDF	TDF AUC ↑ 47%	No dose adjustment needed
NNRTIs		
EFV	LEN AUC↓ 56%	**Do not coadminister.**
ETR	↓ LEN expected	**Do not coadminister.**
DOR	↑ DOR possible	No dose adjustment needed
RPV (IM or PO)	↑ RPV possible	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PIs		
ATV/r	↑ LEN expected	**Do not coadminister.**
ATV/c	LEN AUC ↑ 4-fold	**Do not coadminister.**
DRV/c	DRV/c AUC ↑ 94%	No dose adjustment needed
DRV/r	↑ LEN expected	No dose adjustment needed
Beta-Agonists, Long-Acting Inhaled		
Arformoterol, Formoterol, Indacaterol, Olodaterol, Salmeterol	↔ expected	No dose adjustment needed
Cardiac Medications		
Antiarrhythmics		
Amiodarone	↑ amiodarone expected ↑ LEN possible	**Do not coadminister.**
Digoxin	↑ digoxin expected	Consider alternative ARV or antiarrhythmic. If coadministered, monitor digoxin therapeutic concentration.
Disopyramide	↑ disopyramide expected	**Do not coadminister.**
Dofetilide	↔ expected	No dose adjustment needed
Dronedarone	↑ dronedarone possible ↑ LEN possible	Consider alternative ARV or cardiac medication. If coadministered, monitor for dronedarone-related adverse events.
Flecainide	↔ expected	No dose adjustment needed
Lidocaine	↑ propafenone possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor for antiarrhythmic-related adverse events and monitor concentrations, if available.
Mexiletine	↔ expected	No dose adjustment needed
Propafenone	↑ propafenone possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor for antiarrhythmic-related adverse events and monitor concentrations, if available.
Quinidine	↑ quinidine expected	**Do not coadminister.**
Sotalol	↔ expected	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Beta-Blockers		
Atenolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nebivolol, Timolol	↔ expected	No dose adjustment needed
Calcium Channel Blockers		
Amlodipine, Felodipine, Nifedipine	↑ amlodipine, felodipine expected ↑ nifedipine possible	Monitor and dose adjust according to clinical response and adverse events.
Diltiazem, Verapamil	↑ diltiazem possible ↔ verapamil expected	No dose adjustment needed
Cardiac – Other		
Bosentan	↓ LEN expected	**Do not coadminister.**
Eplerenone	↑ eplerenone expected	**For Post-MI CHF** • Dosing of eplerenone should not exceed 25 mg daily. **For Hypertension** • Initiate at 25 mg once daily. Dosing may be increased to a maximum of 25 mg twice daily.
Ivabradine	↑ ivabradine expected	**Do not coadminister.**
Mavacamten	↓ LEN possible ↑ mavacamten expected	Initiate mavacamten at the recommended starting dose of 5 mg daily in patients who are on stable therapy with LEN. Reduce dose of mavacamten by one level (i.e., 15 to 10 mg, 10 to 5 mg, or 5 to 2.5 mg) in patients who are on mavacamten treatment and intend to initiate LEN.
Ranolazine	↑ ranolazine expected	Limit ranolazine to 500 mg twice daily.
Corticosteroids		
Beclomethasone Inhaled or intranasal **Ciclesonide** Inhaled	↔ expected	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Budesonide, Fluticasone, Mometasone Inhaled or intranasal	↑ glucocorticoids possible	Initiate with the lowest starting dose and titrate carefully and monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events.
Betamethasone Systemic	↑ betamethasone possible ↓ LEN possible	**Do not coadminister.**
Budesonide, Prednisone, Prednisolone Systemic	↑ glucocorticoids expected	Initiate with the lowest starting dose, titrate carefully, and monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events.
Dexamethasone Systemic	↑ dexamethasone expected ↓ LEN expected if used with dexamethasone >16 mg/day	Initiate with the lowest starting dose, titrate carefully, and monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events. **Do not coadminister** with dexamethasone >16 mg/day**.**
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	↑ glucocorticoids possible	Monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events.
Glucose-Lowering		
Canagliflozin	↔ expected	No dose adjustment needed
Saxagliptin	↑ saxagliptin possible	No dose adjustment needed
Dapagliflozin/Saxagliptin	↑ saxagliptin possible	No dose adjustment needed
Herbal Products		
St. John's Wort	↓ LEN expected	**Contraindicated**
Hormonal Therapies—Contraceptives		
Injectable Contraceptives Depot MPA	↑ MPA possible	No dose adjustment needed
Oral Contraceptives (e.g., desogestrel, drospirenone, ethinyl estradiol, levonorgestrel, norgestimate)	↑ contraceptive exposures possible	No dose adjustment needed
Subdermal Implant Contraceptives (e.g., etonogestrel, levonorgestrel)	↑ contraceptive exposures possible	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Transdermal Contraceptives (e.g., ethinyl estradiol/norelgestromin, ethinyl estradiol/levonorgestrel)	↑ contraceptive exposures possible	No dose adjustment needed
Vaginal Ring Contraceptives (e.g., etonogestrel/ethinyl estradiol, segesterone/ethinyl estradiol)	↑ contraceptive exposures possible	No dose adjustment needed
Emergency Contraceptives Levonorgestrel (oral)	↑ levonorgestrel possible	No dose adjustment needed
Hormonal Therapies—Gender Affirming and Menopause		
Estradiol	↔ expected	No dose adjustment needed
5-Alpha Reductase Inhibitors (e.g., dutasteride, finasteride)	↑ dutasteride and finasteride possible	No dose adjustment needed
Testosterone	↑ testosterone possible	No dose adjustment needed
Other Gender-Affirming Medications	↔ goserelin, leuprolide acetate expected	No dose adjustment needed
Menopausal Hormone Replacement Therapy (e.g., conjugated estrogens, drospirenone, estradiol, medroxyprogesterone, progesterone)	↑ estrogen and progesterone possible ↑ drospirenone possible	No dose adjustment needed
Immunosuppressants		
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Lipid-Modifying		
Atorvastatin	↑ atorvastatin possible	No dose adjustment needed
Fluvastatin	↔ expected	No dose adjustment needed
Lomitapide	↑ lomitapide expected	**Contraindicated**
Lovastatin	↑ lovastatin expected	Administer the lowest effective lovastatin dose while monitoring for adverse events.
Pitavastatin	↔ expected	No dose adjustment needed
Pravastatin	↔ expected	No dose adjustment needed

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rosuvastatin	↑ rosuvastatin possible	No dose adjustment needed
Simvastatin	↑ simvastatin expected	Administer the lowest effective simvastatin dose while monitoring for adverse events.
Narcotics and Treatment for Opioid Dependence		
Buprenorphine Sublingual, buccal, or implant	↑ buprenorphine possible	**Initiation of Buprenorphine in Patients Taking LEN** • Titrate buprenorphine dose to desired effect and use the lowest feasible initial dose. **Initiation of LEN in Patients Taking Buprenorphine** • Dose adjustment for buprenorphine may be needed. Monitor for buprenorphine-related adverse events.
Fentanyl	↑ fentanyl possible	Monitor for fentanyl-related adverse events, including potentially fatal respiratory depression. Fentanyl dose reduction may be necessary.
Lofexidine	↔ expected	No dose adjustment needed
Methadone	↑ methadone possible	**Initiation of Methadone in Patients Taking LEN** • Titrate methadone dose to desired effect and use the lowest feasible initial dose. **Initiation of LEN in Patients Taking Methadone** • Dose adjustment for methadone may be needed. Monitor for buprenorphine-related adverse events.
Oxycodone	↑ oxycodone possible	Monitor for opioid-related adverse events, including potentially fatal respiratory depression. Oxycodone dose reduction may be necessary.
Tramadol	↑ tramadol possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors		
Avanafil	↑ avanafil expected	Avanafil dose should not exceed 50 mg once every 24 hours.
Sildenafil	↑ sildenafil expected	**For Treatment of Erectile Dysfunction** • Start with sildenafil 25 mg and monitor for sildenafil-related adverse events. **For Treatment of PAH** • Reduce the dose of sildenafil to 20 mg three times a day when discontinuing treatment with LEN.
Tadalafil	↑ tadalafil expected	**For Treatment of Erectile Dysfunction** • For once-daily use: Consider maximum dose of 2.5 mg daily. If higher dose is needed, consider alternative PDE5 inhibitor. • For use as needed: Consider maximum dose of 10 mg every 72 hours. If higher dosing is needed, consider alternative PDE5 inhibitor. **For Treatment of PAH** • **Do not coadminister.** **For Treatment of Benign Prostatic Hyperplasia** • Consider maximum dose of 2.5 mg daily. Use caution and monitor for AEs if dose increases to 5 mg.
Vardenafil	↑ vardenafil expected	Vardenafil dose should not exceed 5 mg once every 24 hours.
Sedative/Hypnotics		
Benzodiazepines		
Alprazolam, Diazepam, Triazolam	↑ alprazolam expected	Consider lowest dose and monitor for benzodiazepine-related adverse events.
Clonazepam	↑ clonazepam possible	Use with caution and consider alternative benzodiazepines.
Lorazepam, Oxazepam, Temazepam	↔ expected	No dose adjustment needed
Midazolam (Oral), Triazolam	↑ midazolam AUC 259-308%	Use with caution and consider alternative benzodiazepine.

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Orexin Receptor Antagonist		
Daridorexant, Lemborexant, Suvorexant	↑ daridorexant expected ↑ lemborexant expected ↑ suvorexant expected	Maximum recommended daridorexant dose is 25 mg. **Do not coadminister** with lemborexant. Initiate suvorexant dose at 5 mg daily. Suvorexant dose can be increased to 10 mg once per night if the 5 mg dose is not effective. **Do not exceed** 10 mg per night.
Other Sedatives		
Eszopiclone	↑ eszopiclone expected	Consider lowest dose and monitor for eszopiclone-related adverse events.
Zolpidem	↑ zolpidem possible	Consider initiating zolpidem at a low dose.
Miscellaneous Drugs		
Calcifediol	↑ calcifediol possible	No dose adjustment needed
Cisapride	↑ cisapride expected	**Do not coadminister.**
Colchicine	↑ colchicine expected	**For Treatment of Gout Flares** • Administer single colchicine dose of 1.2 mg. Do not repeat dose for at least 3 days. **For Treatment of Familial Mediterranean Fever** • Colchicine dose should not exceed 1.2 mg daily (may be given as 0.6 mg twice a day).
Dronabinol	↔ expected	No dose adjustment needed
Eluxadoline	↔ expected	No dose adjustment needed
Finerenone	↑ finerenone expected	Monitor serum potassium at initiation and during therapy according to finerenone product labeling.
Flibanserin	↑ flibanserin expected	**Contraindicated**
Naloxegol	↑ naloxegol expected	Avoid use; if coadministration is necessary, decrease dosage of naloxegol and monitor for naloxegol-related adverse events.

Table 24g. Drug Interactions Between the Capsid Inhibitor Lenacapavir and Other Drugs (Including Antiretroviral Drugs)

Concomitant Drug Class/ Name	Effect on LEN and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Praziquantel	↑ praziquantel possible	Consider alternative antiretroviral. If coadministration is necessary, monitor for praziquantel-related adverse events.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse event; AUC = area under the curve; ARV = antiretroviral; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CHF = congestive heart failure; CMV = cytomegalovirus; CNS = central nervous system; CV = cardiovascular; CYP = cytochrome P450; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; FTR = fostemsavir; IBA = ibalizumab; IM = intramuscular; INR = international normalized ratio; INSTI = integrase strand transfer inhibitor; QTc = QT corrected for heart rate; LEN = lenacapavir; MI = myocardial infarction; MPA = medroxyprogesterone acetate; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

Updated: September 12, 2024
Reviewed: September 12, 2024

Note: Interactions associated with unboosted atazanavir (ATV), delavirdine (DLV), fosamprenavir (FPV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), nevirapine (NVP), saquinavir (SQV), and tipranavir (TPV) are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding interactions between these drugs and other concomitant drugs.

Rilpivirine (RPV) intramuscular (IM) is not included in this table, because the combination of cabotegravir (CAB) IM plus RPV IM is a two-drug co-packaged product. Therefore, RPV IM is not expected to be used with a protease inhibitor.

PIs		NNRTIs			
		DOR	**EFV**	**ETR**	**RPV**
ATV/c	**PK Data**	↑ DOR expected ↔ ATV expected	↔ EFV expected ↓ ATV possible ↓ COBI possible	↑ ETR possible ↓ ATV possible ↓ COBI possible	↑ RPV PO possible ↔ ATV expected
	Dose	No dose adjustment needed	**ATV/c in ART-Naive Patients** • ATV 400 mg plus COBI 150 mg once daily • **Do not use** coformulated ATV 300 mg/COBI 150 mg. **ATV/c in ART-Experienced Patients** • **Do not coadminister.** No dose adjustment needed for EFV.	**Do not coadminister.**	No dose adjustment needed

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

PIs		NNRTIs			
		DOR	**EFV**	**ETR**	**RPV**
ATV/r	**PK Data**	↑ DOR expected ↔ ATV expected	↔ EFV expected **(ATV 400 mg Plus RTV 100 mg) Once Daily** • ATV concentrations similar to (ATV 300 mg plus RTV 100 mg) without EFV	**(ATV 300 mg Plus RTV 100 mg) Once Daily** • ETR AUC and C_{min} both ↑ ~30% • ↔ ATV AUC and C_{min}	↑ RPV PO possible ↔ ATV expected
	Dose	No dose adjustment needed	**ATV/r in ART-Naive Patients** • (ATV 400 mg plus RTV 100 mg) once daily **ATV/r in ART-Experienced Patients** • **Do not coadminister.** No dose adjustment needed for EFV	No dose adjustment needed	No dose adjustment needed
DRV/c	**PK Data**	↑ DOR expected ↔ DRV expected	↔ EFV expected ↓ DRV possible ↓ COBI possible	**ETR 400 mg Once Daily With (DRV 800 mg Plus COBI 150 mg) Once Daily** • ↔ ETR AUC and C_{min} • ↔ DRV AUC and C_{min} ↓ 56% • COBI AUC ↓ 30% and C_{min} ↓ 66%	↔ DRV expected ↑ RPV PO possible
	Dose	No dose adjustment needed	**Do not coadminister.**	**Do not coadminister.**	No dose adjustment needed

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

PIs		NNRTIs			
		DOR	**EFV**	**ETR**	**RPV**
DRV/r	**PK Data**	↑ DOR expected ↔ DRV expected	**With (DRV 300 mg Plus RTV 100 mg) Twice Daily** • EFV AUC ↑ 21% • ↔ DRV AUC and C_{min} ↓ 31%	**ETR 100 mg Twice Daily With (DRV 600 mg Plus RTV 100 mg) Twice Daily** • ETR AUC ↓ 37% and C_{min} ↓ 49% • ↔ DRV	**RPV 150 mg PO Once Daily With (DRV 800 mg Plus RTV 100 mg) Once Daily** • RPV PO AUC ↑ 130% and C_{min} ↑ 178% • ↔ DRV
	Dose	No dose adjustment needed	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	No dose adjustment needed Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	No dose adjustment needed

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: ART = antiretroviral therapy; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = oral; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

Updated: September 12, 2024
Reviewed: September 12, 2024

Recommendations for managing a particular drug interaction may differ depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication, or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

Information on drug interactions with oral (PO) cabotegravir (CAB) is not included in this table. The CAB PO tablet is not available in retail pharmacies and will be provided directly to people with HIV for short-term use only (PO lead-in and to bridge if intramuscular [IM] administration is delayed).

CAB IM and rilpivirine (RPV) IM are not included in this table because the combination is a two-drug, co-packaged product. Therefore, it is not anticipated that they will be used with PO non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs).

ARV Drugs by Drug Class		INSTIs			
		BIC	**DTG**	**EVG/c**	**RAL**
NNRTIs					
DOR	**PK Data**	↔ DOR and BIC expected	↔ DOR DTG AUC ↑ 36% and C_{min} ↑ 27%	↑ DOR expected ↔ EVG	↔ DOR and RAL expected
	Dose	No dose adjustment needed.	No dose adjustment needed.	No dose adjustment needed.	No dose adjustment needed.
EFV	**PK Data**	↓ BIC expected	**With DTG 50 mg Once Daily** • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, and EFV possible	**With RAL 400 mg Twice Daily** • RAL AUC ↓ 36% and C_{min} ↓ 21% **With RAL 1,200 mg Once Daily** • ↔ RAL AUC and C_{min}

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
	Dose	**Do not coadminister.**	**In Patients Without INSTI Resistance** • DTG 50 mg twice daily **In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance** • Consider alternative combination	**Do not coadminister.**	No dose adjustment needed.
ETR	**PK Data**	↓ BIC expected	**ETR 200 mg Twice Daily Plus DTG 50 mg Once Daily** • DTG AUC ↓ 71% and C_{min} ↓ 88% **ETR 200 mg Twice Daily With (DRV 600 mg Plus RTV 100 mg) Twice Daily and DTG 50 mg Once Daily** • DTG AUC ↓ 25% and C_{min} ↓ 37%	↑ or ↓ EVG, COBI, and ETR possible	**ETR 200 mg Twice Daily Plus RAL 400 mg Twice Daily** • ETR C_{min} ↑ 17% • RAL C_{min} ↓ 34%
	Dose	**Do not coadminister.**	**Do not coadminister** ETR and DTG without concurrently administering ATV/r or DRV/r. **In Patients Without INSTI Resistance** • DTG 50 mg once daily with ETR (concurrently with ATV/r or DRV/r)	**Do not coadminister.**	RAL 400 mg twice daily Coadministration with RAL 1,200 mg once daily **is not recommended.**

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
			In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance • DTG 50 mg twice daily with ETR (concurrently with ATV/r or DRV/r)		
RPV	**PK Data**	No data	**With DTG 50 mg Once Daily** • ↔ DTG AUC and C_{min} ↑ 22% • ↔ RPV PO AUC and C_{min} ↑ 21%	↑ RPV PO possible	↔ RPV PO RAL C_{min} ↑ 27%
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister.**	No dose adjustment needed.
PIs					
ATV/c	**PK Data**	BIC AUC ↑ 306%	No data	Not applicable	No data
	Dose	**Do not coadminister.**	No dose adjustment needed.	**Do not coadminister** two COBI-containing products.	No dose adjustment needed.
ATV/r	**PK Data**	↑ BIC expected	**(ATV 300 mg Plus RTV 100 mg) Once Daily Plus DTG 30 mg Once Daily** • DTG AUC ↑ 62% and C_{min} ↑ 121%	Not applicable	**With (ATV 300 mg Plus RTV 100 mg) Once Daily** • RAL AUC ↑ 41%
	Dose	**Do not coadminister.**	No dose adjustment needed.	**Do not coadminister** RTV and COBI.	No dose adjustment needed.
DRV	**PK Data**	Not applicable	Not applicable	↔ DRV or EVG expected	Not applicable
	Dose	**Do not administer** DRV without RTV or COBI.	**Do not administer** DRV without RTV or COBI.	No dose adjustment needed.	**Do not administer** DRV without RTV or COBI.

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
DRV/c	**PK Data**	BIC AUC ↑ 74%	**DRV/c Plus DTG Once Daily** • ↔ DTG, DRV, and COBI **DTG 50 mg Once Daily and DRV/r Once Daily Switched to DRV/c** • DTG C_{min} ↑ 100%	Not applicable	No data
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister** two COBI-containing products.	No dose adjustment needed.
DRV/r	**PK Data**	No data	**(DRV 600 mg Plus RTV 100 mg) Twice Daily With DTG 30 mg Once Daily** • DTG AUC ↓ 22% and C_{min} ↓ 38%	Not applicable	**With (DRV 600 mg Plus RTV 100 mg) Twice Daily** • RAL AUC ↓ 29% and Cmin ↑ 38%
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister** RTV and COBI.	No dose adjustment needed.

[a] Refer to DTG product label for details.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: ARV = antiretroviral; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; C_{min} = minimum plasma concentration; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir

Appendix A: Key to Acronyms

Updated: September 12, 2024
Reviewed: September 12, 2024

Drug Name Abbreviations

Abbreviation	Definition
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
ATV/c	atazanavir/cobicistat
ATV/r	atazanavir/ritonavir
BIC	bictegravir
CAB	cabotegravir
CAB-LA	long-acting cabotegravir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DRV/c	darunavir/cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
EVG/c	elvitegravir/cobicistat
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitabine
FTR	fostemsavir
IBA	ibalizumab
IDV	indinavir
LA CAB/RPV	long-acting cabotegravir plus rilpivirine

Abbreviation	Definition
LEN	lenacapavir
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
TMP-SMX	trimethoprim-sulfamethoxazole
TMR	temsavir
TPV	tipranavir
TPV/r	tipranavir/ritonavir
ZDV	zidovudine

General Terms

Abbreviation	Definition
17-BMP	beclomethasone 17-monopropionate
ACA	Affordable Care Act
ADAP	AIDS Drug Assistance Program
AE	adverse event
Ag/Ab	antigen/antibody
AHA	American Heart Association
AHC-HRSN	Accountable Health Communities Health-Related Social Needs
Al	aluminum
ALT	alanine aminotransferase
AMP	average manufacturer price
aPR	adjusted prevalence ratio
ART	antiretroviral therapy
ARTAS	Anti-Retroviral Treatment and Access to Services
ARV	antiretroviral
ASP	average sales price
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
AUD	alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
AV	atrioventricular
AWP	average wholesale price
AYA	adolescents and young adults
BMD	bone mineral density
BMI	body mass index
BMT	bone marrow transplant
BUN	blood urea nitrogen
Ca	calcium
$CaCO_3$	calcium carbonate
CBC	complete blood count
CCB	calcium channel blocker
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention

Abbreviation	Definition
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
CI	confidence interval capsid inhibitor
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMS	Centers for Medicare & Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
COC	combined oral contraceptive
CPI-U	consumer price index-urban
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CsA	cyclosporine
CSF	cerebrospinal fluid
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
D/M	dual/mixed
DAA	direct-acting antiviral
DDI	drug–drug interaction
DHA	dihydroartemisinin
DILI	drug-induced liver injury
DM	diabetes mellitus
DMPA	depo-medroxyprogesterone acetate
DOAC	direct oral anticoagulant
DOT	directly observed therapy
DSMB	Data Safety Monitoring Board
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram

Abbreviation	Definition
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FCP	federal price ceiling
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
Fe	iron
FUL	federal upper limit
GAHT	gender-affirming hormone therapy
GFR	glomerular filtration rate
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
H2	histamine type 2
H2RA	H2 receptor antagonist
HAND	HIV-associated neurocognitive disorder
HAV	hepatitis A virus
HbA1C	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCO_3	bicarbonate
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HD	hemodialysis high-dose
HDL	high-density lipoprotein
HDV	hepatitis D virus
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HIV RNA	HIV viral load

Abbreviation	Definition
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVMA/IDSA	HIV Medicine Association of the Infectious Diseases Society of America
HLA	human leukocyte antigen
HMG-CoA	hydroxy-methylglutaryl-coenzyme A
HR	hazard ratio
HRSA	Health Resources and Services Administration
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HSR	hypersensitivity reaction
HTLV-1	human T-lymphotropic virus-1 type I
IC_{50}	median inhibitory concentration
IL	interleukin
IM	intramuscular
IMF	illicitly manufactured fentanyl
IN	integrase
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
ISR	injection site reactions
IUD	intrauterine device
IV	intravenous
K	potassium
LA	long-acting
LDL	low-density lipoprotein
LGBTQ	lesbian, gay, bisexual, transgender, or queer
LLOD	lower limits of detection
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MATE	multidrug and toxin extrusion transporter
MDMA	methylenedioxymethamphetamine
MDR	multidrug resistant
MDR-TB	multidrug-resistant tuberculosis

Abbreviation	Definition
MDRP	Medicaid Drug Rebate Program
MET	motivational enhancement therapy
Mg	magnesium
MHC	major histocompatibility complex
MI	motivational interviewing myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTR	multi-tablet regimen
N/A	not applicable
Na	sodium
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NTD	neural tube defect
OARAC	Office of AIDS Research Advisory Council
OATP	organic anion-transporting polypeptide
OBR	optimized background regimen
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
OI	opportunistic infection
ONDCP	Office of National Drug Control Policy
OR	odds ratio
OTP	opioid treatment program
OUD	opioid use disorder
P	phosphorus
P-gp	p-glycoprotein
PAH	pulmonary arterial hypertension
PBM	pharmacy benefit manager
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
PEP	post-exposure prophylaxis

Abbreviation	Definition
PI	protease inhibitor
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic
PO	orally
PPI	proton pump inhibitor
PR	protease
PRAPARE	Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone
QTc	QT corrected for heart rate
REPC	Retention through Enhanced Personal Contact
RNA	ribonucleic acid
RT	reverse transcriptase
RWHAP	Ryan White HIV/AIDS Program
SAMHSA	Substance Abuse and Mental Health ServicesAdministration
SCr	serum creatinine
SDOH	social determinants of health
SMR	sexual maturity rating
SOT	solid organ transplantation
SPT	skin patch test
SQ	subcutaneous
SSP	syringe service program
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
STR	single-tablet regimen
SUD	substance use disorder
TasP	treatment as prevention
TB	tuberculosis
TC	total cholesterol
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring
TDR	transmitted drug resistance
TG	triglyceride

Abbreviation	Definition
The Panel	The Panel on Antiretroviral Guidelines for Adults and Adolescents
U=U	Undetectable = Untransmittable
UGT	uridine diphosphate glucuronosyltransferase
UGT1	uridine diphosphate glucuronosyltransferase 1 family
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
UW	University of Washington
VL	viral load
VPA	valproic acid
WAC	wholesale acquisition cost
WBC	white blood cell
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health
XDR	extensively drug-resistant
XR	extended release
Zn	zinc

Study and Trial Names

Acronym/Abbreviation	Name
ACTG	AIDS Clinical Trials Group
ADVANCE	Assessing Donor Variability And New Concepts in Eligibility
ARDENT	ACTG A5257 trial
ARTEMIS	Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
CARES	Cabotegravir and Rilpivirine Efficacy and Safety
CoRECT	Cooperative Re-Engagement Controlled Trial
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
D^2EFT	Dolutegravir and Darunavir Evaluation in Adults Failing Therapy
ECHO	Evidence for Contraceptive Options in HIV
ENCORE	Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy
FLAIR	First Long-Acting Injectable Regimen
HPTN	HIV Prevention Trials Network
LATITUDE	Long-Acting Therapy to Improve Treatment Success in Daily LifE
NADIA	Nucleosides And Darunavir/Dolutegravir In Africa
REPRIEVE	Randomized Trial to Prevent Vascular Events in HIV
STaR	Single-Tablet Regimen
START	Strategic Timing of AntiRetroviral Treatment
THRIVE	Targeting HIV Retention and Improved Viral Load Through Engagement
VACS	Veterans Aging Cohort Study
WIHS	Women's Interagency HIV Study

Appendix B. Drug Characteristics Tables

Appendix B, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Updated: September 12, 2024
Reviewed: September 12, 2024

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved coformulated and copackaged antiretroviral regimens for adults with HIV. Not all products are FDA approved for adolescents with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines. Please see the class-specific drug characteristics tables (Appendix B, Tables 3, 4, 5, and 6) for details about the individual drugs included in these products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. The products in this table are listed by drug class and arranged **in alphabetical order** by trade name within each class.

Trade Name (Abbreviation)	**ARV Drugs Included in the Regimen**	**Dosing Recommendation**[a]
INSTI Plus Two NRTIs		
Biktarvy (BIC/TAF/FTC)	Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet PO once daily
Genvoya (EVG/c/TAF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/ emtricitabine 200 mg	One tablet PO once daily with food
Stribild (EVG/c/TDF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir disoproxil fumarate 300 mg/ emtricitabine 200 mg	One tablet PO once daily with food
Triumeq (DTG/ABC/3TC)	Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg	One tablet PO once daily
INSTI Plus One NRTI		
Dovato (DTG/3TC)	Dolutegravir 50 mg/lamivudine 300 mg	One tablet PO once daily

Appendix B, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Trade Name (Abbreviation)	ARV Drugs Included in the Regimen	Dosing Recommendation[a]
INSTI Plus One NNRTI		
Cabenuva (CAB IM and RPV IM)	**Cabenuva 600-mg/900-mg Kit:** • CAB 600-mg/3-mL vial and RPV 900-mg/3-mL vial **Cabenuva 400-mg/600-mg Kit:** • CAB 400-mg/2-mL vial and RPV 600-mg/2-mL vial	**Optional Lead-In With Oral CAB and RPV** • CAB 30 mg PO and RPV 25 mg PO once daily with food for 4 weeks **Monthly IM CAB and RPV** • Loading dose: CAB 600 mg/3 mL IM for 1 dose and RPV 900 mg/ 3 mL IM for 1 dose • Continuation phase: CAB 400 mg/2 mL IM every 4 weeks and RPV 600 mg/2 mL IM every 4 weeks **Every-2-Month IM CAB and RPV** • Loading dose: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM **once monthly** for 2 doses • Continuation phase: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM every 2 months
Juluca (DTG/RPV)	Dolutegravir 50 mg/rilpivirine 25 mg	One tablet PO once daily with food
NNRTI Plus Two NRTIs		
Atripla (EFV/TDF/FTC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
Complera (RPV/TDF/FTC)	Rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily with food
Delstrigo (DOR/TDF/3TC)	Doravirine 100 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily
Odefsey (RPV/TAF/FTC)	Rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet PO once daily with food
Symfi (EFV/TDF/3TC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
Symfi Lo (EFV/TDF/3TC)	Efavirenz 400 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily on an empty stomach, preferably at bedtime

Appendix B, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Trade Name (Abbreviation)	ARV Drugs Included in the Regimen	Dosing Recommendation[a]
PI Plus Two NRTIs		
Symtuza (DRV/c/TAF/FTC)	Darunavir 800 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet PO once daily with food

[a] For dose adjustments in people with renal or hepatic insufficiency, see Appendix B, Table 12. When no food restriction is listed, the product can be taken with or without food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; IM = intramuscularly; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = orally; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 2. Nucleoside Reverse Transcriptase Inhibitor-Based, Fixed-Dose Combination Tablets for Use as Part of an Antiretroviral Regimen

Updated: May 26, 2023
Reviewed: September 12, 2024

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved dual nucleoside reverse transcriptase inhibitor fixed-dose combination (FDC) products for adults with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines. These FDC tablets are not complete regimens and must be administered in combination with other antiretroviral drugs. FDC products that contain zidovudine (ZDV) have been removed from this table. Please refer to the FDA product labels for information regarding ZDV-containing FDCs. Please see the class-specific drug characteristics tables (Appendix B, Tables 3, 4, 5, and 6) for details about the individual drugs contained in these FDC products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. The FDC tablets in this table are listed by trade name.

Trade Name (Abbreviation)	**ARV Drugs Included in the FDC Tablet**	**Dosing Recommendation**[a]
TAF or TDF Plus an NRTI		
Descovy (TAF/FTC)	Tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet PO once daily
Cimduo (TDF/3TC)	Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily
Truvada (TDF/FTC)	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily
Other NRTI-Based, FDC Tablets		
Epzicom (ABC/3TC) **Note:** Generic product is available.	Abacavir 600 mg/lamivudine 300 mg	One tablet PO once daily

[a] For dose adjustments in people with renal or hepatic insufficiency, see Appendix B, Table 12. All FDC tablets listed in this table can be taken without regard to food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; FDC = fixed-dose combination; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; PO = orally; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

Updated: May 26, 2023
Reviewed: September 12, 2024

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved nucleoside reverse transcriptase inhibitor products for adults with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines. The older nucleoside reverse transcriptase inhibitors didanosine (ddI) and stavudine (d4T) have been discontinued in the United States. Zidovudine (ZDV) is no longer used commonly in clinical practice. Therefore, these antiretrovirals have been removed from this table. Please refer to the FDA product label for ZDV for information regarding this drug.

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum/ Intracellular Half-Lives**	**Adverse Events**[b]
Abacavir (ABC) *Ziagen* **Note:** Generic tablet formulation is available.	**Ziagen** • 300-mg tablet • 20-mg/mL oral solution **Generic** • 300-mg tablet • Also available as FDC with 3TC **FDC Tablets That Contain ABC**[c] • Epzicom (ABC/3TC) **STRs That Contain ABC**[d] • Triumeq (DTG/ABC/3TC)	**Ziagen** • ABC 600 mg PO once daily, *or* • ABC 300 mg PO twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain ABC.	Metabolized by alcohol dehydrogenase and glucuronyl transferase 82% of ABC dose is excreted in the urine as metabolites of ABC. Dose adjustment is recommended in people with hepatic insufficiency (see Appendix B, Table 12).	1.5 hours/12–26 hours	People who test positive for HLA-B*5701 are at the highest risk of experiencing HSRs. HLA screening should be done before initiating ABC. For people with a history of HSRs, rechallenge **is not recommended.** Symptoms of HSRs may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (e.g., sore throat, cough, or shortness of breath). Some cohort studies suggest an increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva*	**Emtriva** • 200-mg hard gelatin capsule • 10-mg/mL oral solution **FDC Tablets That Contain FTC[c]** • Descovy (TAF/FTC) • Truvada (TDF/FTC) **STRs That Contain FTC[d]** • Atripla (EFV/TDF/FTC) • Biktarvy (BIC/TAF/FTC) • Complera (RPV/TDF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Stribild (EVG/c/TDF/FTC) • Symtuza (DRV/c/TAF/FTC)	**Emtriva** *Capsule* • FTC 200 mg PO once daily *Oral Solution* • FTC 240 mg (24 mL) PO once daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain FTC.	86% of FTC dose is excreted renally. See Appendix B, Table 12 for dosing recommendations in people with renal insufficiency.	10 hours/ >20 hours	Minimal toxicity Hyperpigmentation/skin discoloration Severe acute exacerbation of hepatitis may occur in people with HBV/HIV coinfection who discontinue FTC.
Lamivudine (3TC) *Epivir* **Note:** Generic products are available.	**Epivir** • 150-mg and 300-mg tablets • 10-mg/mL oral solution **Generic** • 150-mg and 300-mg tablets • Also available as FDC with ABC **FDC Tablets That Contain 3TC[c]** • Cimduo (TDF/3TC) • Epzicom (ABC/3TC)	**Epivir** • 3TC 300 mg PO once daily, *or* • 3TC 150 mg PO twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain 3TC.	70% of 3TC dose is excreted renally. See Appendix B, Table 12 for dose recommendations in people with renal insufficiency.	5–7 hours/ 18–22 hours	Minimal toxicity Severe acute exacerbation of hepatitis may occur in people with HBV/HIV coinfection who discontinue 3TC.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum/ Intracellular Half-Lives**	**Adverse Events**[b]
	STRs That Contain 3TC[d] • Delstrigo (DOR/TDF/3TC) • Dovato (DTG/3TC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC) • Triumeq (DTG/ABC/3TC)				
Tenofovir Alafenamide (TAF) *Vemlidy* **Note:** Vemlidy is available as a 25-mg tablet for the treatment of HBV.	**FDC Tablets That Contain TAF**[c] • Descovy (TAF/FTC) **STRs That Contain TAF**[d] • Biktarvy (BIC/TAF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Symtuza (DRV/c/TAF/FTC)	See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TAF.	Metabolized by cathepsin A See Appendix B, Table 12 for dosing recommendations in people with renal insufficiency.	0.5 hour/ 150–180 hours	Renal insufficiency, Fanconi syndrome, and proximal renal tubulopathy are less likely to occur with TAF than with TDF. Osteomalacia and decreases in BMD are less likely to occur with TAF than with TDF. Severe acute exacerbation of hepatitis may occur in people with HBV/HIV coinfection who discontinue TAF. Diarrhea, nausea, headache Greater weight increase has been reported with TAF than with TDF.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Disoproxil Fumarate (TDF) *Viread* **Note:** Generic product is available.	**Viread** • 300-mg tablet • 40-mg/g oral powder **Generic** • 300-mg tablet **FDC Tablets That Contain TDF[c]** • Cimduo (TDF/3TC) • Truvada (TDF/FTC) **STRs That Contain TDF[d]** • Atripla (EFV/TDF/FTC) • Complera (RPV/TDF/FTC) • Delstrigo (DOR/TDF/3TC) • Stribild (EVG/c/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	**Viread** • TDF 300 mg PO once daily, *or* • 7.5 level scoops of oral powder PO once daily (dosing scoop dispensed with each bottle; one level scoop contains 1 g of oral powder). Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.** See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TDF.	Renal excretion is the primary route of elimination. See Appendix B, Table 12 for dose recommendations in people with renal insufficiency.	17 hours/ >60 hours	Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy Osteomalacia, decrease in BMD Asthenia, headache, diarrhea, nausea, vomiting, flatulence Severe acute exacerbation of hepatitis may occur in people with HBV/HIV coinfection who discontinue TDF.

[a] For dose adjustments in people with renal or hepatic insufficiency, see Appendix B, Table 12. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix B, Table 2 for information about these formulations.

[d] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BMD = bone mineral density; DOR = doravirine; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; PO = orally; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

Updated: September 12, 2024
Reviewed: September 12, 2024

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved non-nucleoside reverse transcriptase inhibitor (NNRTI) products for adults with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines. The older NNRTIs delavirdine (DLV) and nevirapine (NVP) are **not** listed in this table; DLV has been discontinued and NVP is no longer commonly used in clinical practice in the United States.

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum Half-Life**	**Adverse Events**[b]
Doravirine (DOR) *Pifeltro*	**Pifeltro** • 100-mg tablet **STRs That Contain DOR**[c] • Delstrigo (DOR/TDF/3TC)	**Pifeltro** • DOR 100 mg PO once daily See Appendix B, Table 1 for dosing information for Delstrigo.	CYP3A4/5 substrate	15 hours	Nausea Dizziness Abnormal dreams
Efavirenz (EFV) **Note:** The branded product Sustiva has been discontinued.	**Efavirenz** (generic) • 600-mg tablet **STRs That Contain EFV**[c] • Atripla (EFV/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	**Efavirenz** (generic) • EFV 600 mg PO once daily on an empty stomach, preferably at or before bedtime See Appendix B, Table 1 for dosing information for STRs that contain EFV.	Metabolized by CYP2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2B6 and 2C19 inducer	40–55 hours	Rash[d] Neuropsychiatric symptoms[e] Serum transaminase elevations Hyperlipidemia QT interval prolongation Use of EFV may lead to false-positive results with some cannabinoid and benzodiazepine screening assays.
Etravirine (ETR) *Intelence*	**Intelence** • 100-mg and 200-mg tablets	**Intelence** • ETR 200 mg PO twice daily following a meal.	CYP3A4, 2C9, and 2C19 substrate CYP3A4 inducer CYP2C9 and 2C19 inhibitor	41 hours	Rash, including Stevens-Johnson syndrome[d] HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure), have been reported. Nausea

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum Half-Life**	**Adverse Events**[b]
Rilpivirine (RPV) *Edurant*	**Edurant** • 25-mg tablet **STRs That Contain RPV**[c] • Complera (RPV/TDF/FTC) • Juluca (DTG/RPV) • Odefsey (RPV/TAF/FTC) **Copackaged Intramuscular Regimen** • Cabenuva (CAB plus RPV)	**Edurant** • RPV 25 mg PO once daily with food. See Appendix B, Table 1 for dosing information for coformulated and copackaged regimens that contain RPV.	CYP3A4 substrate	PO: 50 hours IM: 13–28 weeks	Rash[d] Depressive disorders, insomnia, headache Hepatotoxicity QT interval prolongation **IM Formulation Only** • Injection site reactions (pain, induration, swelling, nodules) • Rare postinjection reaction (dyspnea, agitation, abdominal cramps, flushing) occurring within a few minutes after RPV IM injection; possibly associated with inadvertent IV administration.

[a] For dose adjustments in people with renal or hepatic insufficiency, see Appendix B, Table 12. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix B, Table 1 for information about these formulations.

[d] Rare cases of Stevens-Johnson syndrome have been reported with the use of most NNRTIs.

[e] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (e.g., suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of people who are receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks, but discontinuation of EFV may be necessary in a small percentage of people. Late-onset neurotoxicities, including ataxia and encephalopathy, have been reported.

Key: 3TC = lamivudine; ARV = antiretroviral; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; FTC = emtricitabine; HSR = hypersensitivity reaction; IM = intramuscular; IV = intravenous; NNRTI = non-nucleoside reverse transcriptase inhibitor; PO = orally; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 5. Characteristics of Protease Inhibitors

Updated: September 12, 2024
Reviewed: September 12, 2024

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved protease inhibitor products for adults with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines. The older protease inhibitors indinavir (IDV) and saquinavir (SQV) have been discontinued in the United States; fosamprenavir (FPV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), and tipranavir (TPV) are no longer used commonly in clinical practice. These agents have been removed from this table. Please refer to the July 10, 2019, version of the guidelines (found in the Adult and Adolescent Antiretroviral Archived Guidelines section of the Archived Guidelines webpage on the Clinicalinfo website) or to the FDA product labels for information regarding these drugs.

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum Half-Life**	**Adverse Events**[b]
Atazanavir (ATV) *Reyataz* (ATV/c) *Evotaz* **Note:** Generic products of ATV are available.	**Reyataz** • 200-mg and 300-mg capsules • 50-mg oral powder/packet **Generic** • 200-mg and 300-mg capsules **Evotaz** • ATV 300-mg/COBI 150-mg tablet	**Reyataz** *In People Without Prior ARV Treatment* • (ATV 300 mg plus RTV 100 mg) PO once daily with food; *or* • ATV 400 mg PO once daily with food. *With TDF or in ARV-Experienced People* • (ATV 300 mg plus RTV 100 mg) PO once daily with food. • Unboosted ATV **is not recommended**. *With EFV in People Without Prior ARV Treatment* • (ATV 400 mg plus RTV 100 mg) PO once daily with food. **Evotaz** • One tablet PO once daily with food.	**ATV** • CYP3A4 inhibitor and substrate • Weak CYP2C8 inhibitor • UGT1A1 inhibitor **COBI** • CYP3A inhibitor and substrate • CYP2D6 inhibitor Dose adjustment is recommended in people with hepatic insufficiency (see Appendix B, Table 12).	7 hours	Indirect hyperbilirubinemia Cholelithiasis Nephrolithiasis Renal insufficiency Serum transaminase elevations Hyperlipidemia (especially with RTV boosting) Skin rash Hyperglycemia Lipodystrophy An increase in serum creatinine may occur when ATV is administered with COBI.

Appendix B, Table 5. Characteristics of Protease Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
		• The use of ATV/c **is not recommended** for people who are taking TDF and who have baseline CrCl <70 mL/min (see Appendix B, Table 12 for the equation for calculating CrCl). For dosing recommendations for people who also are receiving H2 antagonists and PPIs, refer to Table 24a.			PR interval prolongation: First-degree symptomatic AV block has been reported. Use with caution in people who have underlying conduction defects or who are on concomitant medications that can cause PR prolongation.
Darunavir (DRV) *Prezista* (DRV/c) *Prezcobix*	**Prezista** • 600-mg and 800-mg tablets • 100-mg/mL oral suspension **Prezcobix** • DRV 800-mg/COBI 150-mg tablet Also available as part of the STR Symtuza (DRV/c/TAF/FTC)	**Prezista** *In People Without Prior ARV Treatment or ARV-Experienced Treatment With No DRV Mutations* • (DRV 800 mg plus RTV 100 mg) PO once daily with food. *In ARV-Experienced People With One or More DRV Resistance Mutations* • (DRV 600 mg plus RTV 100 mg) PO twice daily with food. Unboosted DRV **is not recommended.** **Prezcobix** • One tablet PO once daily with food. • **Not recommended** for people with one or more DRV resistance-associated mutations. • Coadministering Prezcobix and TDF **is not recommended** for people with baseline CrCl <70 mL/min (see Appendix B, Table 12 for the equation for calculating CrCl). See Appendix B, Table 1 for dosing information for Symtuza.	**DRV** • CYP3A4 inhibitor and substrate • CYP2C9 inducer **COBI** • CYP3A inhibitor and substrate • CYP2D6 inhibitor	15 hours when combined with RTV 7 hours when combined with COBI	Hepatotoxicity Diarrhea, nausea Headache Hyperlipidemia Serum transaminase elevation Hyperglycemia Lipodystrophy An increase in serum creatinine may occur when DRV is administered with COBI. Skin rash: DRV has a sulfonamide moiety; however, incidence and severity of rash are similar in those with or without a sulfonamide allergy—Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported.

Appendix B, Table 5. Characteristics of Protease Inhibitors

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum Half-Life**	**Adverse Events**[b]
Ritonavir (RTV) *Norvir* **Note:** Generic is available. RTV was initially developed as a PI for HIV treatment but is now primarily used at a lower dose of 100 mg once or twice daily as a PK enhancer to increase the concentrations of other PIs.	**Norvir** • 100-mg tablet • 100-mg single packet oral powder Also available as part of the FDC tablet Kaletra (LPV/r)	**As a PK Booster (or Enhancer) for Other PIs** • RTV 100–200 mg PO per day in one or two divided doses (refer to other PIs for specific dosing recommendations) with food.	CYP3A4 > 2D6 substrate Potent CYP3A4 and 2D6 inhibitor Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	3–5 hours	GI intolerance, nausea, vomiting, diarrhea Paresthesia (circumoral and extremities) Hyperlipidemia (especially hypertriglyceridemia) Hepatitis Asthenia Dysgeusia Hyperglycemia Fat maldistribution

[a] For dose adjustments in people with hepatic insufficiency, see Appendix B, Table 12.

[b] Also see Table 20.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FDC = fixed-dose combination; FTC = emtricitabine; GI = gastrointestinal; H2 = histamine H2 receptor; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT1 = uridine diphosphate glucuronyl transferase 1 family

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Updated: September 12, 2024
Reviewed: September 12, 2024

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved integrase strand transfer inhibitor products for adults with HIV. Not all products are FDA-approved for adolescents with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines.

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathways**	**Serum Half-Life**	**Adverse Events**[b]
Bictegravir (BIC)	BIC is available only as a component of the STR Biktarvy (BIC/TAF/FTC).[c]	**Biktarvy** • One tablet PO once daily	CYP3A4 substrate UGT1A1-mediated glucuronidation	~17 hours	Diarrhea Nausea Headache Weight gain
Cabotegravir (CAB)	Available as part of the copackaged IM long-acting regimen Cabenuva (CAB IM and RPV IM) • 400-mg/2-mL vial • 600-mg/3-mL vial Also available as an individual product for IM long-acting pre-exposure prophylaxis Apretude (CAB IM) • 600-mg/3-mL vial Also available in oral tablet formulation Vocabria (CAB PO) • 30-mg tablet • Must be obtained from manufacturer for oral lead-in and oral bridging during administration of Cabenuva (CAB IM/RPV IM)	See Appendix B, Table 1 for dosing information for coformulated and copackaged regimens that contain CAB.	UGT1A1 and UGT1A9-mediated glucuronidation	Oral: 41 hours IM: 6–12 weeks	IM formulation only: Injection site reactions (e.g., pain, induration, swelling, nodules) The following AEs were reported when CAB was administered in combination with RPV: Headache Nausea Abnormal dreams Anxiety Insomnia Depressive disorders Hepatotoxicity

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathways**	**Serum Half-Life**	**Adverse Events**[b]
Dolutegravir (DTG) *Tivicay*	**Tivicay** • 50-mg tablet **STRs That Contain DTG**[c] • Dovato (DTG/3TC) • Juluca (DTG/RPV) • Triumeq (DTG/ABC/3TC)	**In People Without Prior ARV Treatment or ARV-Experienced People Who Had Never Received INSTIs** • DTG 50 mg PO once daily **In People Without Prior ARV Treatment or ARV-Experienced People Who Had Never Received INSTIs When Coadministered With EFV, FPV/r, TPV/r, or Rifampin** • DTG 50 PO mg twice daily **In INSTI-Experienced People With Certain INSTI Mutations (See Product Label) or With Clinically Suspected INSTI Resistance** • DTG 50 mg PO twice daily See Appendix B, Table 1 for dosing information for STRs that contain DTG.	UGT1A1-mediated glucuronidation Minor substrate of CYP3A4	~14 hours	Insomnia Headache Depressive disorders and suicidal ideation (rare; usually occurs in people with preexisting psychiatric conditions) Weight gain Hepatotoxicity HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury), have been reported.

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Elvitegravir (EVG)	EVG is only available as a component of an STR tablet that also contains COBI, FTC, and either TDF or TAF. **STRs That Contain EVG[c]** • Genvoya (EVG/c/TAF/FTC) • Stribild (EVG/c/TDF/FTC)	**Genvoya** • One tablet PO once daily with food. • See Appendix B, Table 12 for recommendations on dosing in persons with renal insufficiency. **Stribild** • One tablet PO once daily with food. • **Not recommended** for people with baseline CrCl <70 mL/min (see Appendix B, Table 12 for the CrCl calculation equation).	**EVG** • CYP3A and UGT1A1/3 substrate **COBI** • CYP3A inhibitor and substrate • CYP2D6 inhibitor	EVG/c: ~13 hours	Nausea Diarrhea Depression and suicidal ideation (rare; usually occurs in people with preexisting psychiatric conditions)
Raltegravir (RAL) *Isentress* *Isentress HD*	**Isentress** • 400-mg tablet • 100-mg single-use packet for oral suspension **Isentress HD** • 600-mg tablet	**Isentress** • 400 mg PO twice daily *With Rifampin* • 800 mg PO twice daily **Isentress HD** *In People Without Prior ARV Treatment or ARV-Experienced People With Virologic Suppression on a Regimen Containing RAL 400 mg Twice Daily* • 1,200 mg (two 600-mg tablets) PO once daily *With Rifampin* • **Not recommended**	UGT1A1-mediated glucuronidation	~9 hours	Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis Nausea Headache Diarrhea Pyrexia CPK elevation, muscle weakness, and rhabdomyolysis Weight gain Insomnia

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathways**	**Serum Half-Life**	**Adverse Events**[b]
					Depression and suicidal ideation (rare; usually occurs in people with preexisting psychiatric conditions)

[a] For dose adjustments in people with hepatic insufficiency, see Appendix B, Table 12. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; IM = intramuscular; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PO = orally; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; UGT1 = uridine diphosphate glucuronyl transferase 1 family

Appendix B, Table 7. Characteristics of the Fusion Inhibitor

Updated: May 26, 2023
Reviewed: September 12, 2024

The following table includes dose recommendations for the U.S. Food and Drug Administration (FDA)–approved fusion inhibitor. For additional information regarding the use of this medication in adolescents with HIV, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendation**	**Serum Half-Life**	**Elimination**	**Adverse Events**[a]
Enfuvirtide (T-20) *Fuzeon*	**Fuzeon** • Injectable; supplied as lyophilized powder. • Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL. • Refer to prescribing information for storage instruction.	**Fuzeon** • T-20 90 mg/1 mL SQ twice daily	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.	Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost all people Increased incidence of bacterial pneumonia HSR occurs in <1% of people. Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. **Rechallenge is not recommended.**

[a] Also see Table 20.

Key: HSR = hypersensitivity reaction; SQ = subcutaneous; T-20 = enfuvirtide

Appendix B, Table 8. Characteristics of the CCR5 Antagonist

Updated: May 26, 2023
Reviewed: September 12, 2024

The following table includes dose recommendations for the U.S. Food and Drug Administration (FDA)–approved CCR5 antagonist. For additional information regarding the use of this medication in adolescents with HIV, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	**Selzentry** • 150-mg and 300-mg tablets • 20-mg/1-mL oral solution	**Selzentry** • MVC 150 mg PO twice daily when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers), including PIs (except TPV/r) • MVC 300 mg PO twice daily when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • MVC 600 mg PO twice daily when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take MVC without regard to food.	14–18 hours	CYP3A4 substrate	Abdominal pain Cough Dizziness Musculoskeletal symptoms Pyrexia Rash Upper respiratory tract infections Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions Orthostatic hypotension, especially in people with severe renal insufficiency

[a] For dose adjustments in people with hepatic insufficiency, see Appendix B, Table 12.

[b] Also see Table 20.

Key: CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; T-20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 9. Characteristics of the CD4 Post-Attachment Inhibitor

Updated: May 26, 2023
Reviewed: September 12, 2024

The following table includes dose recommendations for the U.S. Food and Drug Administration (FDA)–approved CD4 post-attachment inhibitor. Ibalizumab is not FDA approved for use in adolescents with HIV.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Serum Half-Life**	**Elimination/ Metabolic Pathway**	**Adverse Events**[a]
Ibalizumab (IBA) *Trogarzo*	**Trogarzo** • Single-dose 2-mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab	**Trogarzo** • Administer a single loading dose of IBA 2,000-mg IV infusion over 30 minutes, followed by a maintenance dose of IBA 800-mg IV infusion over 15 minutes or IV push over 30 seconds every 2 weeks. • See prescribing information for additional instructions for preparing, storing, and administering IBA, and for monitoring people who are receiving IBA.	~64 hours	Not well defined	Diarrhea Dizziness Nausea Rash HSRs, including anaphylaxis and infusion-related reactions, have been reported.

[a] Also see Table 20.

Key: HSR = hypersensitivity reaction; IBA = ibalizumab; IV = intravenous

Appendix B, Table 10. Characteristics of the gp120 Attachment Inhibitor

Updated: May 26, 2023
Reviewed: September 12, 2024

The following table includes dose recommendations for the U.S. Food and Drug Administration (FDA)–approved gp120 attachment inhibitor. Fostemsavir is not FDA approved for use in adolescents with HIV.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Serum Half-Life**	**Elimination/ Metabolic Pathway**	**Adverse Events**[a]
Fostemsavir (FTR) *Rukobia*	• 600-mg extended-release tablets	• FTR 600 mg PO twice daily	11 hours	Hydrolysis (esterases), CYP3A4	Nausea Transaminase elevation; transient bilirubin elevation Sleep disturbance, dizziness QTc prolongation was seen at four times the recommended dose. Use with caution in people with preexisting heart disease, QTc prolongation, or concomitant use of medications that may prolong QTc interval.

[a] also see Table 20.

Key: CYP = cytochrome P; FTR = fostemsavir; PO = orally; QTc = corrected QT interval

Appendix B, Table 11. Characteristics of the Capsid Inhibitor

Updated: September 12, 2024
Reviewed: September 12, 2024

The following table includes dose recommendations for the U.S. Food and Drug Administration (FDA)–approved capsid inhibitor. Lenacapavir is not FDA approved for use in adolescents with HIV.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Serum Half-Life**	**Elimination/ Metabolic Pathway**	**Adverse Events**[a]
Lenacapavir (LEN) *Sunlenca*	• 300-mg tablet • Single-dose 463.5-mg/1.5-mL vial for injection	**Initiation Option 1** • Day 1: 927 mg SQ x 1 dose + 600 mg PO x 1 dose • Day 2: 600 mg PO x 1 dose **Initiation Option 2** • Day 1: 600 mg PO x 1 dose • Day 2: 600 mg PO x 1 dose • Day 8: 300 mg PO x 1 dose • Day 15: 927 mg SQ x 1 dose **Maintenance Dosing** • 927 mg by SQ injection every 6 months from the date of the last injection (+/-2 weeks) **Note:** Each SQ dose requires two injections.	PO: 10–12 days SQ: 8–12 weeks	Substrate of P-glycoprotein, CYP3A (minor), UGT1A1 (minor) CYP3A4 inhibitor (moderate)	Injection site reactions, including nodules and induration Nausea, diarrhea, headache

[a] Also see Table 20.

Key: CYP = cytochrome P; LEN = lenacapavir; PO = orally; SQ = subcutaneous

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Updated: September 12, 2024
Reviewed: September 12, 2024

Not all products are Food and Drug Administration (FDA)–approved for adolescents with HIV. For information regarding the use of these medications in adolescents with HIV, including weight limitations and additional dosage forms, please consult FDA product labeling or Appendix A in the Pediatric Antiretroviral Guidelines.

The older antiretroviral drugs fosamprenavir (FPV), lopinavir/ritonavir (LPV/r) , nelfinavir (NFV), nevirapine (NVP), tipranavir (TPV), and zidovudine (ZDV) have been removed from this table. Please refer to the FDA product labels for these drugs for recommendations on dosing in adults and adolescents with renal or hepatic insufficiency.

See the reference section at the end of this table for creatinine clearance calculation formulas and criteria for Child-Pugh classification.

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Recommendations for FDCs based on CrCl level are outlined in the table below.			
NRTIs			
Abacavir (ABC) *Ziagen*	ABC 300 mg PO twice daily *or* ABC 600 mg PO once daily	No dose adjustment necessary.	*Child-Pugh Class A:* ABC 200 mg PO twice daily (use oral solution) *Child-Pugh Class B or C:* **Contraindicated**
Abacavir/Lamivudine (ABC/3TC) *Epzicom*	One tablet PO once daily	Not FDA recommended if CrCl <30 mL/min due to the 3TC component. **Note:** There is insufficient evidence to recommend for or against the use of full-dose 3TC in people with CrCl <30 mL/min. Some Panel members use full-dose 3TC to allow people to remain on the FDC product. See the 3TC entry for more information.	*Child-Pugh Class A:* People with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these people. *Child-Pugh Class B or C:* **Contraindicated** due to the ABC component
Emtricitabine (FTC) *Emtriva*		**Dose by Formulation** **CrCl (mL/min)** / **Capsule** / **Solution** 30–49[b] / No dose adjustment necessary.	No dose recommendation.

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**			**Dosing in Adults With Hepatic Impairment**
	FTC 200-mg oral capsule once daily *or* FTC 240-mg (24-mL) oral solution once daily **Note:** There is insufficient evidence to recommend for or against the use of full-dose, daily FTC in people with CrCl <30 mL/min who are not on HD. To allow people to remain on certain TAF-containing FDC products, some Panel members use full-dose, daily FTC in people with CrCl 15–29 mL/min who are not on HD.	15–29 (see **Note**)	200 mg every 72 hours	80 mg every 24 hours	
		<15 (not on HD) (see **Note**)	200 mg every 96 hours	60 mg every 24 hours	
		On HD[b]	No dose adjustment necessary. On HD days, administer after dialysis.		
Lamivudine[c] (3TC) *Epivir*	3TC 300 mg PO once daily *or* 3TC 150 mg PO twice daily **Note:** PK and safety data are limited on the use of 3TC doses higher than those recommended by the FDA in people with CrCl <30 mL/min. Clinicians may consider using the nearest available tablet strength (100 mg or 150 mg), as outlined in the "Alternative Dose" column **(BIII)** (see rationale[d]). There is insufficient evidence to recommend for or against the use of full-dose 3TC in people with CrCl <30 mL/min. Some Panel members use full-dose 3TC to allow people to remain on certain ABC and/or DTG-containing FDC products.	**CrCl (mL/min)**	**Epivir Label Dose**	**Alternative Dose**[d]	No dose adjustment necessary
		15–29 (see **Note**)	1 × 150 mg, then 100 mg every 24 hours	100–150 mg every 24 hours	
		5–14 (see **Note**)	1 × 150 mg, then 50 mg every 24 hours	100–150 mg every 24 hours	
		<5 or on HD (see **Note**)	1 × 50 mg, then 25 mg every 24 hours	100–150 mg every 24 hours	

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults With Renal Insufficiency		Dosing in Adults With Hepatic Impairment
Tenofovir Alafenamide (TAF) *Vemlidy*	Vemlidy is available as a 25-mg tablet for the treatment of HBV.	**CrCl (mL/min)**	**Dose**	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B or C:* **Not recommended**
		<15 (not on HD)	**Not recommended**	
		On HD	No dose adjustment necessary. On HD days, administer after dialysis.	
Tenofovir Alafenamide/ Emtricitabine (TAF/FTC) *Descovy*	TAF for HIV treatment is only available as a component of FDC tablets (i.e., in Descovy, Genvoya, Odefsey, Biktarvy, and Symtuza). • TAF 10 mg PO daily with EVG/c (Genvoya) or DRV/c (Symtuza) • TAF 25 mg PO daily in other FDC tablets	**CrCl (mL/min)**	**Dose**	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C*: No dose recommendation
		15–29	**Not recommended** **Note:** There is insufficient evidence to recommend for or against the use of full-dose, daily FTC in people with CrCl <30 mL/min. To allow people to remain on the FDC product, some Panel members use full-dose FTC in people with CrCl 15–29 mL/min.	
		<15 (not on HD)	**Not recommended**	
		On HD	No dose adjustment necessary. On HD days, administer after dialysis.	
Tenofovir Disoproxil Fumarate (TDF) *Viread*	TDF 300 mg PO once daily	**CrCl (mL/min)**	**Dose**	No dose adjustment necessary
		30–49	300 mg every 48 hours	
		10–29	300 mg twice weekly (every 72–96 hours)	
		<10 (not on HD)	No recommendation	
		On HD	300 mg every 7 days (administer after completion of HD)	
Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) *Truvada*	One tablet PO once daily	**CrCl (mL/min)**	**Dose**	No dose recommendation
		30–49	One tablet every 48 hours	
		<30 or on HD	FDC of TDF/FTC **not recommended**	

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults With Renal Insufficiency		Dosing in Adults With Hepatic Impairment
Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) *Cimduo*	One tablet PO once daily	**CrCl (mL/min)**	**Dose**	No dose recommendation
		<50 or on HD	FDC of TDF/3TC **not recommended**	
NNRTIs				
Doravirine (DOR) *Pifeltro*	DOR 100 mg PO once daily	No dose adjustment required in mild, moderate, or severe renal impairment. Has not been studied in individuals with ESRD or on HD.		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied
Doravirine/Tenofovir Disoproxil Fumarate/ Lamivudine (DOR/TDF/3TC) *Delstrigo*	One tablet PO once daily	FDC of DOR/TDF/3TC **not recommended** if CrCl <50 mL/min or on HD		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied
Efavirenz (EFV) *Sustiva*	EFV 600 mg PO once daily on an empty stomach, preferably at bedtime	No dose adjustment necessary		No dose recommendation; use with caution in people with hepatic impairment.
Efavirenz/Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	One tablet PO once daily on an empty stomach, preferably at bedtime	FDC of EFV/TDF/FTC **not recommended** if CrCl <50 mL/min or if on HD		No dose recommendation; use with caution in people with hepatic impairment.
Efavirenz 600 mg/ Tenofovir Disoproxil Fumarate/ Lamivudine (EFV/TDF/3TC) *Symfi*	One tablet PO once daily on an empty stomach, preferably at bedtime	FDC of EFV/TDF/3TC **not recommended** if CrCl <50 mL/min or if on HD		**Not recommended** for people with moderate or severe hepatic impairment. Use with caution in people with mild hepatic impairment.
Efavirenz 400 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi Lo*	One tablet PO once daily on an empty stomach, preferably at bedtime	FDC of EFV/TDF/3TC **not recommended** if CrCl <50 mL/min or if on HD		**Not recommended** for people with moderate or severe hepatic impairment. Use with caution in people with mild hepatic impairment.

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Etravirine (ETR) *Intelence*	ETR 200 mg PO twice daily	No dose adjustment necessary	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine (RPV PO) *Edurant*	RPV 25 mg PO once daily with food	No dose adjustment necessary	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine IM Plus Cabotegravir IM (RPV IM and CAB IM) *Cabenuva*	**Monthly Dosing** • Loading dose: RPV 900 mg/3 mL IM × 1 dose and CAB 600 mg/3 mL IM × 1 dose • Continuation phase: RPV 600 mg/2 mL IM every 4 weeks and CAB 400 mg/2 mL IM every 4 weeks **Every-2-Months Dosing** • Loading dose: RPV 900 mg/3 mL IM and CAB 600 mg/3 mL IM monthly for 2 doses • Continuation phase: RPV 900 mg/3 mL IM and CAB 600 mg/3 mL IM every 2 months	No dose adjustment necessary for mild or moderate renal impairment For people with severe renal impairment or on HD, increase monitoring for adverse events.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults With Renal Insufficiency	Dosing in Adults With Hepatic Impairment
Rilpivirine/Tenofovir Alafenamide/Emtricitabine (RPV/TAF/FTC) *Odefsey*	One tablet PO once daily with food	**In People With CrCl 15–29 mL/min** • **Not recommended** • **Note:** There is insufficient evidence to recommend for or against the use of full-dose, daily FTC in people with CrCl <30 mL/min. To allow people to remain on the FDC product, some Panel members use full-dose, daily FTC in people with CrCl 15–29 mL/min. **In People With CrCl <15 mL/min (not on HD)** • **Not recommended** **In People on Chronic HD** • No dose adjustment necessary. On HD days, administer after dialysis.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine (RPV/TDF/FTC) *Complera*	One tablet PO once daily with food	FDC of RPV/TDF/FTC **not recommended** if CrCl <50 mL/min or on HD	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine/Dolutegravir (RPV/DTG) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary In people with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
PIs			
Atazanavir (ATV) *Reyataz*	ATV 400 mg PO once daily with food *or* (ATV 300 mg plus RTV 100 mg) PO once daily with food	**In People Without Prior ARV Treatment on HD** • (ATV 300 mg plus RTV 100 mg) once daily with food. **In ARV-Experienced People on HD** • ATV and ATV/r **are not recommended.**	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B:* ATV 300 mg once daily (unboosted) for people without prior ARV treatent *Child-Pugh Class C:* **Not recommended** RTV boosting **is not recommended** in people with hepatic impairment.

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Atazanavir/Cobicistat (ATV/c) *Evotaz*	One tablet PO once daily with food	**If Used With TDF** • **Not recommended** if CrCl <70 mL/min	**Not recommended** in people with hepatic impairmen.
Darunavir (DRV) *Prezista*	**In People Without Prior ARV Treatment or ARV-Experienced Treatment With No DRV Mutations** • (DRV 800 mg plus RTV 100 mg) PO once daily with food. **In ARV-Experienced People With at Least One DRV Resistance Mutation** • (DRV 600 mg plus RTV 100 mg) PO twice daily with food.	No dose adjustment necessary	*In People With Mild-to-Moderate Hepatic Impairment:* No dose adjustment *In People With Severe Hepatic Impairment:* **Not recommended**
Darunavir/Cobicistat (DRV/c) *Prezcobix*	One tablet PO once daily with food	**If Used With TDF** • **Not recommended** if CrCl <70 mL/min	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Darunavir/Cobicistat/ Tenofovir Alafenamide/ Emtricitabine (DRV/c/TAF/FTC) *Symtuza*	One tablet PO once daily with food	**In People With CrCl 15–29 mL/min** • **Not recommended** • **Note:** There is insufficient evidence to recommend for or against the use of full-dose, daily FTC in people with CrCl <30 mL/min. To allow people to remain on the FDC product, some Panel members use full-dose, daily FTC in people with CrCl 15–29 mL/min. **In People With CrCl <15 mL/min (not on HD)** • **Not recommended** **In People on Chronic HD** • No dose adjustment necessary. On HD days, administer after dialysis.	**Not recommended** for people with severe hepatic impairment

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Ritonavir (RTV) *Norvir*	**As a PI-Boosting Agent** • RTV 100–400 mg PO per day with food.	No dose adjustment necessary	Refer to recommendations for the primary (i.e., boosted) PI.
INSTIs			
Bictegravir/Tenofovir Alafenamide/Emtricitabine (BIC/TAF/FTC) *Biktarvy*	One tablet PO once daily	**In People With CrCl 15–29 mL/min** • **Not recommended** • **Note:** There is insufficient evidence to recommend for or against the use of full-dose, daily FTC in people with CrCl <30 mL/min. To allow people to remain on the FDC product, some Panel members use full-dose, daily FTC in people with CrCl 15–29 mL/min. **In People With CrCl <15 mL/min (not on HD)** • **Not recommended** **In People on Chronic HD** • No dose adjustment necessary. On HD days, administer after dialysis.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Cabotegravir (CAB PO) *Vocabria*	**Treatment (As Optional Oral Lead-In or As Oral Bridging)** • CAB 30 mg PO once daily, given with RPV 25 mg PO, with food before switching to CAB IM and RPV IM **Pre-exposure Prophylaxis (Optional Oral Lead-In)** • CAB 30 mg PO once daily before switching to CAB IM	No dose adjustment necessary	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Cabotegravir (CAB IM) *Apretude*	**Pre-exposure Prophylaxis** • Loading dose: CAB 600 mg/3 mL IM monthly for 2 doses • Continuation phase: CAB 600 mg/3 mL IM every 2 months	No dose adjustment necessary	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation
Cabotegravir IM plus Rilpivirine IM (CAB IM plus RPV IM) *Cabenuva*	**Monthly Dosing** • Loading dose: CAB 600 mg/3 mL IM × 1 dose and RPV 900 mg/3 mL IM × 1 dose • Continuation phase: CAB 400 mg/2 mL IM every 4 weeks and RPV 600 mg/2 mL IM every 4 weeks **Every 2-Month Dosing** • Loading dose: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM monthly for 2 doses • Continuation phase: CAB 600 mg/3 mL IM and RPV 900 mg/ 3 mL IM every 2 months	No dose adjustment necessary for mild or moderate renal impairment For people with severe renal impairment or on HD, increase monitoring for adverse events.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation
Dolutegravir (DTG) *Tivicay*	DTG 50 mg PO once daily *or* DTG 50 mg PO twice daily	No dose adjustment necessary	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Dolutegravir/Abacavir/ Lamivudine (DTG/ABC/3TC) *Triumeq*	One tablet PO once daily	Not FDA recommended if CrCl <30 mL/min due to the 3TC component **Note:** There is insufficient evidence to recommend for or against the use of full-dose 3TC in people with CrCl <30 mL/min. Some Panel members use full-dose 3TC to allow people to remain on the FDC product.[d]	*Child-Pugh Class A:* People with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these people. *Child-Pugh Class B or C:* **Contraindicated** due to the ABC component

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Dolutegravir/Lamivudine (DTG/3TC) *Dovato*	One tablet PO once daily	Not FDA recommended if CrCl <30 mL/min due to 3TC component **Note:** There is insufficient evidence to recommend for or against the use of full-dose 3TC in people with CrCl <30 mL/min. Some Panel members use full-dose 3TC to allow people to remain on the FDC product.[d]	*Child-Pugh Class C:* **Not recommended**
Dolutegravir/Rilpivirine (DTG/RPV) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary In people with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Elvitegravir/Cobicistat/ Tenofovir Alafenamide/ Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	One tablet PO once daily with food	**In People With CrCl 15–29 mL/min** • **Not recommended** • **Note:** There is insufficient evidence to recommend for or against the use of full-dose, daily FTC in people with CrCl <30 mL/min. To allow people to remain on the FDC product, some Panel members use full-dose, daily FTC in people with CrCl 15–29 mL/min. **In People With CrCl <15 mL/min (not on HD)** • **Not recommended** **In People on Chronic HD** • No dose adjustment necessary. On HD days, administer after dialysis.	*In People With Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In People With Severe Hepatic Insufficiency:* **Not recommended**
Elvitegravir/Cobicistat/ Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/c/TDF/FTC) *Stribild*	One tablet PO once daily with food	EVG/c/TDF/FTC **should not be initiated** in people with CrCl <70 mL/min. Discontinue EVG/c/TDF/FTC if CrCl declines to <50 mL/min while on therapy.	*In People With Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In People With Severe Hepatic Insufficiency:* **Not recommended**

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults With Renal Insufficiency	Dosing in Adults With Hepatic Impairment
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL 400 mg PO twice daily (using Isentress formulation) *or* RAL 1,200 mg PO once daily (using Isentress HD formulation only)	No dose adjustment necessary	*In People With Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In People With Severe Hepatic Insufficiency:* No recommendation
Fusion Inhibitor			
Enfuvirtide (T-20) *Fuzeon*	T-20 90 mg SQ twice daily	No dose adjustment necessary	No dose adjustment necessary
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	The recommended dose differs based on concomitant medications and potential for drug–drug interactions. See Appendix B, Table 8 for detailed dosing information.	**In People With CrCl <30 mL/min or People Who Are on HD** *Without Potent CYP3A Inhibitors or Inducers* • MVC 300 mg twice daily; if postural hypotension occurs, reduce to MVC 150 mg twice daily *With Potent CYP3A Inducers or Inhibitors* • **Not recommended**	No dose recommendations. MVC concentrations will likely be increased in people with hepatic impairment.
CD4 Post-Attachment Inhibitor			
Ibalizumab (IBA) *Trogarzo*	Loading dose: IBA 2,000 mg IV Maintenance dose: IBA 800 mg IV every 2 weeks	No dose adjustment recommended	No recommendation
gp-120 Attachment Inhibitor			
Fostemsavir (FTR) *Rukobia*	FTR 600 mg PO twice daily	No dose adjustment recommended	No dose adjustment recommended

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults With Renal Insufficiency	Dosing in Adults With Hepatic Impairment
Capsid Inhibitor			
Lenacapavir (LEN) *Sunlenca*	**Initiation Option 1** • Day 1: 927 mg SQ x 1 dose plus 600 mg PO x 1 dose • Day 2: 600 mg PO x 1 dose **Initiation Option 2** • Day 1: 600 mg PO x 1 dose • Day 2: 600 mg PO x 1 dose • Day 8: 300 mg PO x 1 dose • Day 15: 927 mg SQ x 1 dose **Maintenance Dosing** • 927 mg by SQ injection every 6 months from the date of the last injection (+/-2 weeks)	No dose adjustment recommended	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation

[a] Refer to Appendix B, Tables 1–10 for additional dosing information.

[b] The prescribing information for FTC (Emtriva) recommends adjusted doses for people with CrCl 30–49 mL/min and people on hemodialysis. However, the prescribing information for several FDC products that contain FTC (including Descovy, Biktarvy, Genvoya, and Odefsey) recommends that the standard dose (FTC 200 mg) can be given once daily in these people. The recommendations in this table incorporates the dosing guidance from the FDC products.

[c] The prescribing information for 3TC (Epivir) recommends dosage adjustment from 300 mg once daily to 150 mg once daily for people with CrCl 30–49 mL/min. However, the prescribing information for several FDC products that contain 3TC (including Epzicom, Dovato, and Triumeq) recommends no dose adjustment for CrCl 30–49 mL/min. The recommendation in this table incorporates the dosing guidance from the FDC products.

[d] Use of 3TC doses higher than those recommended by the FDA for people with CrCl <30 mL/min has been reported in clinical practice [1-4] and endorsed in the Guidelines for Chronic Kidney Disease in People With HIV for many years [5]; limited published literature has supported the safety of this practice [2,3]. 3TC has a wide therapeutic index with no established correlation between elevated concentrations and AEs. Serious AEs, such as lactic acidosis and severe hematologic toxicities, have been reported in rare cases; however, these effects typically occurred when 3TC was used in combination with older NRTIs (such as didanosine, stavudine, zidovudine). Clinicians may consider using the nearest available tablet strength (100 mg or 150 mg) to avoid the need for 3TC oral solution, thereby simplifying ARV regimens and facilitating adherence **(BIII).** See the Alternative Dose column in 3TC table entry. There is insufficient evidence to recommend for or against the use of full-dose 3TC in people with CrCl <30 mL/min. Some Panel members use full-dose 3TC to allow people to remain on certain FDC products.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse effect; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus;

Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

HD = hemodialysis; IBA = ibalizumab; IM = intramuscular; INSTI = integrase strand transfer inhibitor; IV = intravenous; LEN = lenacapavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PK: pharmacokinetic; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Creatinine Clearance Calculation	
Male: $\frac{(140 - age\ in\ years) \times weight\ in\ kg}{72 \times serum\ creatinine}$	**Female:** $\frac{(140 - age\ in\ years) \times weight\ in\ kg \times 0.85}{72 \times serum\ creatinine}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy[a]	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total Bilirubin, *or*	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34–50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified Total Bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin Time (Seconds Prolonged), *or*	<4	4–6	>6
International Normalized Ratio (INR)	<1.7	1.7–2.3	>2.3

[a] **Encephalopathy Grades**

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin is used for people who have Gilbert's syndrome or who are taking atazanavir.

Child-Pugh Classification	Total Child-Pugh Score[a]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[a] Sum of points for each component of the Child-Pugh Score.

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1. Bohjanen P, Johnson M, Szczech L, et al. Steady-state pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with end-stage renal disease receiving chronic dialysis. *Antimicrob Agents Chemother*. 2002;46(8):2387-2392. Available at: https://pubmed.ncbi.nlm.nih.gov/12121909.

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4. Wood B, Pozniak A. Dosing lamivudine or emtricitabine in renal impairment: new data confirm it's time for updated guidance! *AIDS*. 2021;35(8):1305-1307. Available at: https://pubmed.ncbi.nlm.nih.gov/34076616.

5. Lucas G, Ross M, Stock P, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(9):e96-e138. Available at: https://academic.oup.com/cid/article/59/9/e96/422813.

JS 44 (Rev. 10/20)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

American Academy of HIV Medicine, et al.
[see addendum for additional plaintiffs]

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Omar Gonzalez-Pagan, Lambda Legal Defense and Education Fund, Inc., 120 Wall St., 19th Floor, New York, New York 10005, 212-809-8585
[see addendum for additional counsel]

DEFENDANTS

Health Resources and Services Administration, et al.
[see addendum for additional defendants]

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question *(U.S. Government Not a Party)*
- ☒ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 835 Patent - Abbreviated New Drug Application
- ☐ 840 Trademark
- ☐ 880 Defend Trade Secrets Act of 2016

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit (15 USC 1681 or 1692)
- ☐ 485 Telephone Consumer Protection Act
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
5 U.S.C. §§ 705-706; 42 U.S.C. § 18116; U.S. Const., amends. I and V

Brief description of cause:
Plaintiffs seek declaratory and preliminary and permanent injunctive relief against Defendants' policies as violative of the APA, ACA, and Constitutic

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE: June 10, 2026

SIGNATURE OF ATTORNEY OF RECORD: /s/ Omar Gonzalez-Pagan

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

American Academy of HIV Medicine, et al. v. Health Resources and Services Administration, et al.

Addendum 1 to Civil Cover Sheet

List of Plaintiffs

American Academy of HIV Medicine

HIV Medicine Association, a division of the Infectious Diseases Society of America

International Association of Providers of AIDS Care

Jennifer K. Brody, MD

Christopher B. Fox, NP

American Academy of HIV Medicine, et al. v. Health Resources and Services Administration, et al.

Addendum 2 to Civil Cover Sheet

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American Academy of HIV Medicine, et al. v. Health Resources and Services Administration, et al.

Addendum 3 to Civil Cover Sheet

List of Defendants:

Health Resources and Services Administration;

Thomas J. Engels, in his official capacity as the Administrator of the Health Resources and Services Administration

U.S. Department of Health and Human Services

Robert F. Kennedy, Jr., in his official capacity as Secretary of the U.S. Department of Health and Human Services

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

1. **Title of case (name of first party on each side only)** American Academy of HIV Medicine, et al. v. Health Resources and Services Administration, et al.

2. **Category in which the case belongs based upon the numbered nature of suit code listed on the civil cover sheet. (See local rule 40.1(a)(1)).**

☐ **I.** **160, 400, 410, 441, 535, 830*, 835*, 850, 880, 891, 893, R.23, REGARDLESS OF NATURE OF SUIT.**

☑ **II.** **110, 130, 190, 196, 370, 375, 376, 440, 442, 443, 445, 446, 448, 470, 751, 820*, 840*, 895, 896, 899.**

☐ **III.** **120, 140, 150, 151, 152, 153, 195, 210, 220, 230, 240, 245, 290, 310, 315, 320, 330, 340, 345, 350, 355, 360, 362, 365, 367, 368, 371, 380, 385, 422, 423, 430, 450, 460, 462, 463, 465, 480, 485, 490, 510, 530, 540, 550, 555, 560, 625, 690, 710, 720, 740, 790, 791, 861-865, 870, 871, 890, 950.**

***Also complete AO 120 or AO 121. for patent, trademark or copyright cases.**

3. **Title and number, if any, of related cases. (See local rule 40.1(g)). If more than one prior related case has been filed in this district please indicate the title and number of the first filed case in this court.**

N/A

4. **Has a prior action between the same parties and based on the same claim ever been filed in this court?**

YES ☐ **NO** ☑

5. **Does the complaint in this case question the constitutionality of an act of congress affecting the public interest? (See 28 USC §2403)**

YES ☐ **NO** ☑

If so, is the U.S.A. or an officer, agent or employee of the U.S. a party?

YES ☐ **NO** ☐

6. **Is this case required to be heard and determined by a district court of three judges pursuant to title 28 USC §2284?**

YES ☐ **NO** ☑

7. **Do all of the parties in this action, excluding governmental agencies of the United States and the Commonwealth of Massachusetts ("governmental agencies"), residing in Massachusetts reside in the same division? - (See Local Rule 40.1(d)).**

YES ☑ **NO** ☐

A. **If yes, in which division do all of the non-governmental parties reside?**

Eastern Division ☑ **Central Division** ☐ **Western Division** ☐

B. **If no, in which division do the majority of the plaintiffs or the only parties, excluding governmental agencies, residing in Massachusetts reside?**

Eastern Division ☐ **Central Division** ☐ **Western Division** ☐

8. **If filing a Notice of Removal - are there any motions pending in the state court requiring the attention of this Court? (If yes, submit a separate sheet identifying the motions)**

YES ☐ **NO** ☐

(PLEASE TYPE OR PRINT)
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