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)

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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 24, 2026
Reviewed: September 24, 2026

September 24, 2026

The Panel for the Use of Antiretroviral Agents in Adults and Adolescents With HIV (the Panel) has updated the guidelines on the use of antiretroviral therapy (ART) for the treatment of people with HIV.

Note: In August 2026, the U.S. Food and Drug Administration approved bictegravir/lenacapavir (Bixlenvo) for the treatment of HIV. The Panel is reviewing the available information, which will be addressed in a future update.

Sections Added to the Guidelines

Principles of Antiretroviral Therapy

A new section on the Principles of Antiretroviral Therapy has been added to outline the core principles to consider when selecting antiretroviral (ARV) regimens for the treatment of HIV and how to apply these principles in the context of initial therapy, regimen optimization, or virologic failure.

Knowledge Gaps

A new subsection of key "Knowledge Gaps" has been added to the end of select revised sections of the guidelines.

Content Removed From the Guidelines

The guidelines previously included tables outlining select drug–drug interactions associated with ARV medications; however, the Panel now refers readers to the Liverpool HIV Drug Interaction Checker for formal drug–drug interaction guidance. The last versions of the drug–drug interaction tables remain available in the Archived Guidelines. The remaining Drug–Drug Interactions section has been updated to include pharmacokinetic mechanisms related to islatravir drug interactions and a new section on drug–drug interactions with long-acting ARV medications.

Key Revisions to the Guidelines

What to Start

Updates made to the What to Start chapter include the following:

- Based on the DOLCE study, the two-drug ARV regimen of dolutegravir (DTG)/lamivudine (3TC) is now recommended regardless of baseline plasma HIV viral load. See *Recommended Initial Regimens for Most People With HIV*.
- The two-drug combinations of boosted darunavir (DRV) plus 3TC or emtricitabine (FTC) are now included as options for *Initial ARV Regimens for Certain Clinical Scenarios*.

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:

- The Panel provided a list of ARV drugs that **are not recommended** for regimen optimization in the setting of viral suppression due to factors such as serious adverse effects, high pill burden, or low barrier to resistance.
- Expanded discussion on considerations for hepatitis B and HIV when prescribing ARV regimens that do not include tenofovir.
- Added the two-drug ARV regimen doravirine (DOR)/islatravir (ISL) as an optimization strategy for people with ongoing viral suppression and no history of prior virologic failure or resistance to DOR or ISL.
- Added new guidance noting that DTG/3TC or a boosted protease inhibitor plus 3TC or FTC **are not recommended** as switch strategies for people with historical M184V/I mutations.

Interruption of Antiretroviral Therapy

Formerly titled *Discontinuation or Interruption of Antiretroviral Therapy,* the Interruption of Antiretroviral Therapy section was renamed to reflect the importance of ART continuity. Additional updates include the following:

- Expanded discussion regarding considerations for interruptions of oral ART, long-acting (LA) injectable ART, and regimens containing both oral and LA ARVs.

Adolescents and Young Adults With HIV

Updates made to the Adolescents and Young Adults With HIV section include the following:

- Expanded discussion of differences between the management of people with perinatally and non–perinatally acquired HIV, as well as factors that affect HIV care outcomes.
- Expanded discussion on factors (e.g., developmental changes, mental health, substance use, unstable housing, trauma) that are faced by some adolescents and young adults (AYA), as well as the importance of addressing these factors to improve engagement in care and treatment success.
- Added discussion of population-specific adherence strategies, LA ART, treatment considerations for AYA with drug resistance, and transitions from pediatric to adult care.

Substance Use Disorders and HIV

Updates made to the Substance Use Disorders and HIV section include the following:

- Added discussion emphasizing the importance of routine screening for substance use disorders and co-occurring mental health disorders and that ongoing substance use **is not a contraindication** to ART.
- Expanded discussion of polysubstance use, chemsex, unstable housing, opioid adulterants, and other factors that affect HIV care outcomes.
- Added discussion of LA ART for people with substance use disorders and updated the table on Medications for Treatment of Substance Use Disorders.
- Added discussion of medetomidine, an adulterant added to illicit opioids that has led to an outbreak of overdoses. Medetomidine is a CYP3A, 2D, and 2E substrate that may interact with some ARV drugs.

Women With HIV

Updates made to the Women With HIV section include the following:

- Updated published data on the use of LA CAB/RPV during pregnancy and provided guidance on strategies and viral load monitoring if LA CAB/RPV is used during pregnancy.
- Added discussion on ART use and infant feeding options postpartum for women of reproductive potential as recommended by the Perinatal Guidelines.
- Added discussion on special considerations for menopause and comorbidities in the context of HIV care.

Hepatitis B Virus (HBV)/HIV Coinfection

Updates to the HBV/HIV Coinfection section include the following:

- Added recommendation that people with HIV and chronic HBV should be tested for hepatitis D virus infection.
- Clarified that, in certain situations, tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) alone (without 3TC or FTC) can be used as the only drug with HBV activity; TAF or TDF alone for HBV treatment should be used in combination with an effective ARV regimen.
- Highlighted that ISL-containing ARV regimens are **contraindicated** with 3TC and FTC.
- Expanded discussion and recommendations on HBV-specific considerations when initiating or transitioning to tenofovir-sparing ART.

Cost Considerations and Antiretroviral Therapy

Updates made to the Cost Considerations and Antiretroviral Therapy section include the following:

- Added recommendations on assessing and addressing cost-related barriers to ART while ensuring that cost-driven regimen changes do not compromise virologic efficacy.
- Expanded discussion of coverage changes, payer-driven barriers, Medicare coverage, generic and hybrid ART options, LA ART costs, 340B, and Ryan White HIV/AIDS Program supports.
- Added two new tables with cash-pay estimates for recommended initial and optimization ART regimens (Tables 22a and 22b), including generic and hybrid options, and updated Table 22c to include National Average Drug Acquisition Cost benchmarks alongside Wholesale Acquisition Cost and Average Wholesale Price for individual ARV agents, coformulations, and single-tablet regimens.

Other Updates

Minor updates have been made throughout the following sections of the guidelines:

- Introduction
- Baseline Evaluation
- Laboratory Testing for Initial Assessment and Monitoring of People With HIV
- Treatment Goals
- Hepatitis C Virus/HIV Coinfection
- Appendix A: Drug Characteristics Tables
- Appendix B: Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

May 27, 2026

In March 2026, the American College of Cardiology (ACC)/American Heart Association(AHA)/Multisociety published an updated Dyslipidemia Management Guideline, which includes new recommendations specifically for people with HIV. Given that the new recommendations for statin therapy in people with HIV were developed by experts in dyslipidemia management, the Panel will retire its Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People With HIV section and defer to the ACC/AHA/Multisociety Dyslipidemia Management Guideline for statin guidance. The Panel will provide further considerations on the role of statins and other strategies for primary prevention of atherosclerotic cardiovascular disease for people with HIV as part of a future update of the Cardiovascular Complications section of the Guidelines. Until this update occurs, an overview of statin therapy recommendations relevant to people with HIV is available in the Update on Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People With HIV section.

PANEL ROSTER

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Reviewed: August 24, 2026

Roster 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 (the Panel), a working group of the National Institutes of Health Office of AIDS Research Advisory Council.

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FINANCIAL DISCLOSURE

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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, 2025, to March 31, 2026

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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, 2025, to March 31, 2026

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INTRODUCTION

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Antiretroviral therapy (ART) for the treatment of HIV has improved steadily since the advent of potent combination therapy in 1996. Effective ART has significantly reduced HIV-associated morbidity and mortality and has transformed HIV into a chronic condition with life expectancy approaching that of people without HIV.[1,2] Additionally, sustained viral suppression achieved through ART effectively prevents the risk of sexual HIV transmission.[3-5]

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 evidence-based HIV treatment and management recommendations for adults and adolescents with HIV in the United States.

The Panel reviews new evidence and updates recommendations when needed and on an ongoing basis. These guidelines include recommendations on laboratory evaluations and monitoring, treatment goals, benefits of ART and considerations when initiating therapy, ART for the prevention of HIV transmission, choice of the initial ART regimen, management of nonadherence, virologic failure and drug resistance, optimizing antiretroviral (ARV) regimens, management of adverse effects and drug interactions, and special ART-related considerations in specific populations. As people with HIV are living longer, age-related and chronic comorbidities have become increasingly important considerations. Accordingly, these guidelines also address comorbidity-related topics, such as cardiovascular and metabolic complications associated with HIV and ART.

The 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 the most updated recommendations on ART use during pregnancy and postpartum, clinicians should refer to the Perinatal Guidelines.

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.[6-9]

These guidelines represent current knowledge on the use of ARV drugs. Because the science of HIV evolves rapidly, the availability of new ARVs and new clinical data may change therapeutic options and preferences. It should be noted that 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 Clinicalinfo 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 clinical scenarios. 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 HIV care. The Panel encourages both the development of protocols and patient participation in well-designed Institutional

Review Board–approved clinical trials. To address these research needs, key unanswered questions are included at the end of updated chapters to guide future research priorities.

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) medications for the treatment of HIV in adults and adolescents in the United States.
Panel Members	The U.S. Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (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 HHS agencies: Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are nongovernmental scientific members from academia or clinical practice, with expertise in such areas as HIV and antiretroviral therapy (ART) clinical care, research, virologic failure and drug resistance, adolescent medicine, HIV immunology, viral hepatitis, women's health, biostatistics, and pharmacology. 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. Nongovernmental 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. Panel members lead or serve on up to four writing teams in drafting and revising the guidelines chapters. See the Panel Roster for a list of current Panel members. On occasion, the Panel invites outside consultants with expertise in specific topics (e.g., HIV-2, transplantation, pharmacology) to assist in writing the guidelines.
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. The latest version of the Financial Disclosure list is available on the Clinicalinfo website.
Users of the Guidelines	HIV treatment providers, infectious disease specialists, other health care professionals, and trainees.
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. When sufficient data are not available to provide guidance, the Panel occasionally makes recommendations based on expert opinion.
Recommendation Grading	As described in Table 2 below

Table 1. Outline of the Guidelines Development Process

Topic	Comment
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. To be included in the guidelines, a recommendation must be endorsed by a majority of voting members. Recommendations endorsed by the Panel are included in the guidelines.
Other Guidelines	These guidelines focus on 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 women of childbearing potential and pregnant women. 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 Clinicalinfo website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the Clinicalinfo website.
Public Comments	A 2-week public comment period follows the release of the updated guidelines on the Clinicalinfo 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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PRINCIPLES OF ANTIRETROVIRAL THERAPY

Updated: September 24, 2026
Reviewed: September 24, 2026

Core Principles for Selection of the Ideal Antiretroviral Therapy for the Treatment of HIV
• **High Potency:** A highly potent ARV regimen that fully suppresses HIV in the plasma will improve health, decrease the risk of viral replication and drug resistance, and prevent HIV transmission. • **High Barrier to Resistance:** ARV medications with a high barrier to resistance decrease the risk of developing drug resistance. • **Regimen Individualization:** Regimens should be individualized based on ARV treatment history, prior use of ARV medications for pre- or post-exposure prophylaxis, comorbidities, ARV-associated toxicities, resistance testing results, the potential for drug–drug interactions, and individual barriers to care and preference.

Key: ARV = antiretroviral

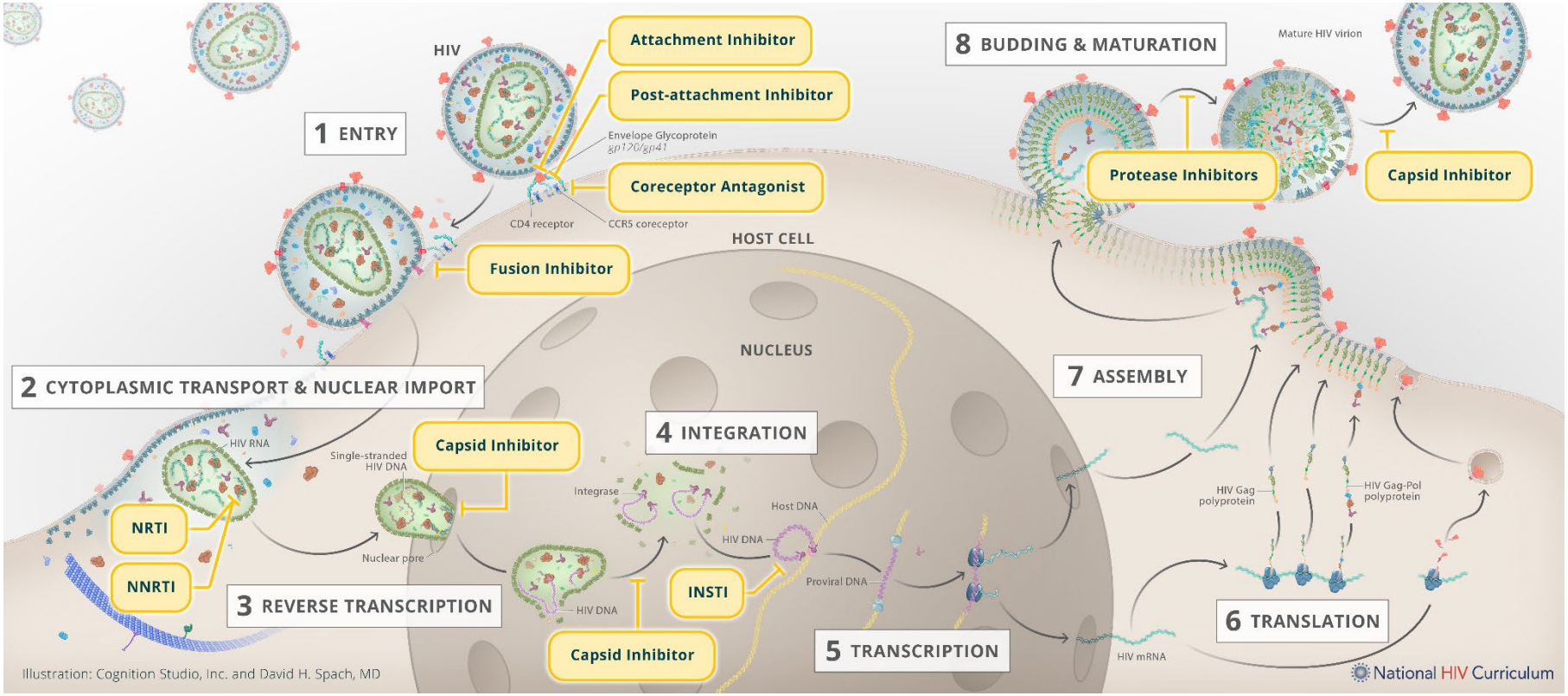
Introduction

The development of effective antiretroviral therapy (ART) that can both control HIV infection within an individual and prevent HIV transmission sexually and perinatally has been one of the most important therapeutic advances in the history of medicine. From the first licensed antiretroviral (ARV) medication, zidovudine (AZT or ZDV) in 1987 to the present, treatment strategies have evolved from single-drug therapy to highly effective two- and three-drug regimens. With more than 25 currently available agents in 2026, many of which are coformulated, people with HIV can now achieve viral control, taking as little as a single daily tablet (see the Drug Characteristics Tables). Long-acting (LA) injectable ART (cabotegravir plus rilpivirine) can now be given monthly or every other month, and once-weekly oral regimens are on the horizon. This remarkable progress reflects an evolving understanding of the principles of ART. Although ART effectively suppresses HIV replication in plasma, leading to substantial immune reconstitution and recovery, continuous treatment is required to maintain these health benefits, as interruption of therapy will result in viral rebound. Based on these advances, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends ART for all people with HIV to reduce the morbidity and mortality associated with HIV **(AI)** and to prevent HIV transmission to sexual partners and infants **(AI).** ART should be initiated as soon as possible after HIV diagnosis **(AII)** (see Initiation of Antiretroviral Therapy). These guidelines aim to support prescribers in selecting effective ARV regimens grounded in the principles outlined above and informed by clinical evidence.

Mechanisms of Antiretroviral Drug Activity

The HIV life cycle is now well characterized, as illustrated in Figure 1 below. Infection of host CD4 T lymphocyte (CD4) cells and subsequent production of infectious virus requires several sequential steps: (1) cell entry, (2) cytoplasmic transport and nuclear import, (3) reverse transcription, (4) integration into the host genome, (5) proviral transcription, (6) translation of viral proteins and glycoproteins, (7) assembly, and (8) budding and maturation. Currently approved ARVs target some of these steps in the HIV life cycle. Entry inhibitors interfere with viral binding to CD4 receptors (attachment and post-attachment inhibitors) or block the chemokine receptor CCR5 (co-receptor antagonist). Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) all inhibit reverse transcriptase, the enzyme that converts viral RNA into DNA. Capsid inhibitors act at multiple stages, including preventing transport of the viral capsid containing proviral DNA into the nucleus. Integrase strand transfer inhibitors (INSTIs) block integration of viral DNA into the host genome. Protease inhibitors (PIs) disrupt the processing of viral proteins and glycoproteins, impairing proper assembly of infectious viral particles.

Figure 1. Life Cycle of HIV and Drug Targets for Antiretroviral Drugs



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Illustration: Cognition Studio, Inc., and David H. Spach, M.D., University of Washington

Goals of Therapy

Optimal use of ARVs requires understanding the goals of therapy. The primary goal is to suppress plasma viral load (or HIV-1 RNA) to levels below the limit of detection ("undetectable"). HIV-1 RNA levels are measured using real-time polymerase chain reaction assays and reported as copies/mL on both absolute and logarithmic scales. Commercially available assays can quantify levels as low as 20 copies/mL. Virologic failure is defined as the inability to achieve or maintain viral suppression at an HIV RNA level <200 copies/mL. Achieving and maintaining viral suppression dramatically reduces HIV-related morbidity and mortality, including complications of late-stage disease (e.g., opportunistic infections, wasting, AIDS-related malignancies), while also reducing the risk of non-AIDS events (e.g., cardiovascular events) and HIV transmission to others.

History of Antiretroviral Therapy

Viral suppression in plasma was difficult to achieve and maintain early in the treatment era. Initial therapy with AZT or other NRTIs alone or in combination rarely led to full viral suppression and therefore the rapid emergence of drug resistance, with virologic and clinical failure, was inevitable. Similar outcomes occurred when a single active agent was added to existing agents for which drug resistance had already developed. The introduction of new drug classes, particularly PIs in 1995, enabled the adoption of potent three-drug regimens; by enabling consistent viral suppression, these three-drug regimens were associated with dramatically improved outcomes. However, successful outcomes were often limited by intolerance, toxicities, drug–drug interactions, dosing complexity (e.g., large pill burden, multiple daily doses, food requirements), and suboptimal medication adherence. Over time, ARVs became more potent and were associated with less toxicity, fewer drug–drug interactions, and simpler dosing requirements. The latter led to the availability of increasing numbers of fixed-dose combinations (single tablets containing more than one drug) and single-tablet regimens (i.e., a single tablet containing multiple drugs that together make a full ARV regimen). In addition, some new ARVs have longer half-lives, requiring less frequent dosing. Today, durable viral suppression can be achieved with single-tablet regimens, including some two-drug regimens, as well as LA agents.

Core Principles of Regimen Selection

For people with HIV, the best ARV regimen is one that is potent, has a high barrier to resistance, and is both simple to take and well tolerated. These principles are reflected in current treatment guidelines and are discussed individually below.

Potency, Barrier to Resistance, and Durability

The selection of ARV regimens with high **potency** and high **barrier to resistance** results in longer durability. Virologic failures are typically driven by insufficient potency of the regimen or insufficient adherence, leading to the emergence of drug resistance (see Virologic Failure).

A highly potent regimen that fully suppresses HIV will decrease the risk of viral replication and the likelihood of development of drug resistance. This principle influences what agents can be used in two- and three-drug combination regimens. Select two-drug regimens with newer agents can be highly effective, whereas older dual-NRTI regimens were unable to achieve viral suppression (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression and What to Start).

Using ARVs with a high “barrier to resistance” decreases the likelihood that the virus will develop or accumulate mutations that lead to drug resistance. This is an important consideration because the reverse transcriptase enzyme is error prone, leading to frequent mutations, some of which confer a selective advantage in the presence of specific ARVs, reducing drug activity. Resistance mutations can emerge against all classes of ARVs and often confer cross-resistance within the drug class. Over time, newer agents within classes have been developed with resistance profiles that are both distinct from earlier agents and require mutations that are less likely to develop. For example, early NNRTIs (e.g., efavirenz) were broadly compromised by single mutations, whereas newer generations (e.g., doravirine) each have unique resistance profiles. Unlike low-barrier-to-resistance ARVs, for which resistance can develop in weeks, for high-barrier ARVs (e.g., boosted PIs and second-generation INSTIs [i.e., bictegravir, dolutegravir]), resistance mutations infrequently emerge, typically only after ongoing exposure in the setting of persistent viremia.

Individualization and Optimization

Ultimately, the selection of an optimal regimen needs to be individualized to the person with HIV. Factors to consider include prior history of ARV use for treatment or prevention, potential barriers to adherence,

comorbidities (e.g., hepatitis B virus [HBV], renal disease), concomitant medications that may result in drug–drug interactions or overlapping toxicities, and patient preferences.

Ideal agents have limited toxicities. Earlier ARV drugs had substantial side effects (e.g., gastrointestinal intolerance, neuropsychiatric symptoms) and toxicities (e.g., neuropathy or lipodystrophy) that impaired quality of life, which led to suboptimal adherence. These side effects are much less common with newer ARVs.

Some comorbidities also influence regimen selection. People with HBV and HIV require concurrent treatment of both HIV and HBV with highly active agents, the latter typically being treated with a regimen that includes tenofovir with or without emtricitabine or lamivudine (or uses entecavir with an active non-tenofovir-containing ARV regimen) (see Hepatitis B Virus/HIV Coinfection). Additional comorbidities may also affect regimen choice, including renal insufficiency, cardiovascular disease, metabolic syndrome, and others (see Adverse Effects of Antiretroviral Medications and the Cardiovascular and Metabolic Complications in People With HIV chapter).

Pregnancy introduces pharmacokinetic considerations (including altered protein binding) and safety considerations for the fetus (see the Perinatal Guidelines).

Drug–drug interactions must also be considered when selecting an ARV regimen, including those involving hepatitis C therapies, antimycobacterial agents, chemotherapy, statins, direct oral anticoagulants, polyvalent cation supplements (e.g., calcium, iron), and acid-reducing agents (see the Liverpool HIV Drug Interaction Checker).

Before choosing a regimen, the prescriber should explore the individual's barriers and preferences in a nonjudgmental discussion. Understanding a person's level of pill aversion and/or challenges with pill size, internalized or external stigma, and the presence of safe storage sites may influence regimen choice (see Adherence to the Continuum of Care). Transportation challenges to the clinic and insurance coverage may impact regimen choice. Preferences for injectable versus oral therapy or daily dosing versus less frequent dosing should be considered. Importantly, mental health conditions or active substance use disorders are **not contraindications** to treatment in a person who is engaged in care (see Substance Use Disorders and HIV). Lastly, costs borne by a person with HIV can be an important barrier to ART initiation and use; incorporating a multidisciplinary approach to link people with HIV to insurance options and additional available services is critical (see Cost Considerations and Antiretroviral Therapy). Ultimately, because of these many challenges, access to continuous, uninterrupted therapy is a privilege afforded to those with stable insurance, housing, and transportation. Without these supports in place, medication interruptions occur. Operational barriers at clinics, such as cost and mental health conditions or substance use, are also key reasons for interrupted care. Clinics should work hard to mitigate these barriers and utilize robust community-based navigation rather than label people with HIV as non-adherent without reviewing their own practices.

Applying the Principles of ART

The principles of ART derived from randomized clinical trials inform all aspects of treatment and apply to options considered for initial therapy, for switching from one suppressive regimen to another, as well as for virologic failure. Treatment in each of these settings is discussed in detail in the following sections: What to Start, Optimizing Antiretroviral Therapy in the Setting of Viral Suppression, and Virologic Failure. Therapeutic options in each scenario are primarily recommended based upon evidence-based efficacy and safety data. Selecting among the options requires individualization based upon special considerations, ranging from regimen dosing and route of administration, adverse effect profile, drug–drug and drug–food interactions, comorbidities, underlying drug resistance, costs borne by the person with HIV, and individual barriers to care and preference. Examples of how these key considerations are incorporated into recommendations for each treatment scenario are summarized below, with details in the respective treatment sections.

- **What to Start:** The ultimate choice is impacted by a host of factors, including, but not limited to, patient preference, transmitted drug resistance, comorbidities (e.g., chronic HBV, renal disease, and tuberculosis), potential for drug–drug interactions, and exposure to ARVs as part of a pre-exposure prophylaxis regimen.
- **Optimizing Antiretroviral Therapy in the Setting of Viral Suppression:** In the absence of any underlying resistance to the drugs included in the new regimen, any regimen recommended for treatment-naive individuals is likely to be effective. In addition, if no resistance is present and no evidence of chronic HBV is found, several two-drug regimens are effective. Although switches in therapy can occur in the setting of an underlying drug-resistant virus, such changes need to be made with caution and preferably in consultation with experts in the field.
- **Virologic Failure:** Despite careful selection, regimen failure can occur. Several factors can contribute to the inability to achieve or loss of viral suppression, including suboptimal adherence, drug resistance, impaired drug absorption, and drug–drug interactions. When adherence challenges are suspected, clinicians should work with the person with HIV to identify underlying barriers and implement strategies to address them, including assessing options to improve access to clinical and supportive services to enhance engagement in care. Regimen switches in the setting of virologic failure (i.e., viral load repeatedly ≥200 copies/mL despite high levels of adherence) should be based on results from cumulative drug resistance testing and will ideally include a fully active high-barrier-to-resistance drug with at least one other active agent, or, if necessary, consideration can be given to using only partially active NRTIs. If a fully active high-barrier drug is not available, the goal is to create a regimen with at least two, and preferably three, fully active agents from other classes.

Overall, the evolution of ART toward potent, well-tolerated, low–pill burden or injectable regimens represents a major scientific achievement, with continued advances anticipated.

BASELINE EVALUATION

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Every person with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation performed, and should be counseled regarding HIV. The medical history should also include any history of antiretroviral (ARV) use for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis. The goals of this initial evaluation are to confirm the diagnosis of HIV, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV 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 Update for Providers Who Care 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 can then 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 or as soon as feasible 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 and physical assessments performed during initial patient visits can be used to assess HIV-related conditions and other comorbidities, and assist in the selection of ARV regimens (see Laboratory Testing):

- HIV antigen/antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection)
- CD4 T lymphocyte (CD4) cell count
- Plasma HIV RNA (viral load)
- Complete blood count; chemistry profile, including glucose, blood urea nitrogen and creatinine, liver enzymes and bilirubin, and urinalysis
    - If random blood glucose level is abnormal, fasting glucose should be obtained.
- Serum lipids (if random levels are abnormal, fasting lipids should be obtained)
- Hepatitis A, B, and C virus serologies
- Genotypic drug-resistance testing **(AII).** Standard genotypic drug-resistance testing involves testing for mutations in the reverse transcriptase and protease genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is suspected or if the person has ever used long-acting cabotegravir as PrEP or received an INSTI-based regimen for post-exposure prophylaxis, genotypic resistance testing also should include the integrase gene (see Drug-Resistance Testing).
    - In people with confirmed HIV RNA levels between 201 copies/mL and 500 copies/mL, drug-resistance testing may not be successful but should still be considered (see Drug-Resistance Testing).
- HLA-B*5701 test (if abacavir is being considered)
- Screening tests for sexually transmitted infections (STIs), opportunistic infections, and cancer should be performed as recommended in the HIVMA/IDSA's Primary Care Guidance Update for

Providers Who Care for Persons With HIV[1] and the Adult and Adolescent Opportunistic Infections Guidelines.[2]

- Height, weight, and the corresponding body mass index
- Pregnancy testing (for those with reproductive potential), if not already performed

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 accelerate the time to viral suppression. Rapid ART initiation also reduces the time during which people with newly diagnosed HIV can transmit HIV. It is critical to outline a clear plan for a comprehensive clinical visit soon after ART initiation, especially for people without a reliable contact method. Rapid ART initiation is appropriate for most people with newly diagnosed HIV. Most laboratory tests discussed above should be obtained prior to ART initiation, but the test results need not be available before the first prescription of ART. Below are some considerations regarding key test results.

- **HIV RNA and CD4 Count:** HIV RNA will provide information on pretreatment viral load, and CD4 count will determine the need for prophylaxis against certain opportunistic infections (see Adult and Adolescent Opportunistic Infections Guidelines).[2]
- **Laboratory Testing (e.g., complete blood count, renal function tests, liver enzymes):** A clinician should review the results as soon as possible.
- **Genotypic Resistance Testing:** Results should be reviewed as soon as possible with adjustments of the ART regimen, if needed (see What to Start and Drug-Resistance Testing).
- **Viral Hepatitis Screening:** If results are pending, a regimen with activity against hepatitis B virus (i.e., tenofovir alafenamide or tenofovir disoproxil fumarate with emtricitabine or lamivudine) should be selected (see What to Start and Hepatitis B Virus/HIV Coinfection).
- **STI Screening:** Testing should be ordered at the initial visit, with results reviewed as soon as possible.

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 person's readiness and commitment for lifelong 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 (see Table 20 in Adherence to the Continuum of Care). 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 for people not on ART, due to ongoing risk of HIV transmission. People with HIV should be informed that maintaining a plasma HIV RNA level of <200 copies/mL with ART, including any measurable value below this threshold, prevents sexual transmission of HIV to their partners **(AII).** This concept may be recognized as Undetectable = Untransmittable or U=U.

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. Understanding why the person with HIV is changing to a new health care provider is also critical to support engagement in care and ART adherence.

In the rare occasion that a person with HIV declines to initiate or reinitiate ART, it is critical to encourage regular follow-up (e.g., every 3–6 months) with a clinical provider and other available

services. Benefits of ART should be discussed at all visits. Table 4 in the Laboratory Testing section provides guidance for laboratory monitoring if ART is deferred.

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LABORATORY TESTING

Laboratory Testing for Initial Assessment and Monitoring of People With HIV

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Reviewed: September 24, 2026

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.

Two surrogate markers have been used to monitor people with HIV: (1) plasma HIV RNA (viral load) to assess the level of HIV viremia and (2) CD4 T lymphocyte (CD4) cell 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 integrase strand transfer inhibitor (INSTI) resistance is a concern due to potential transmitted resistance or previous use of an INSTI for pre-exposure prophylaxis (e.g., long-acting cabotegravir), post-exposure prophylaxis, or treatment, providers should ensure that genotypic resistance testing also includes 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 and Early (Acute or Recent) HIV Infection sections. A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure if a person 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 people should not be prescribed ABC. People should be screened for hepatitis B virus (HBV) 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. Before initiating nucleoside reverse transcriptase inhibitor (NRTI)–sparing or NRTI-limited ARV regimens, HBV serology testing should be performed in people who are not known to have chronic HBV (see Hepatitis B Virus/HIV Coinfection). The rationale for and utility of some of these laboratory tests are discussed in the corresponding sections of the guidelines.

Currently available newer ARVs are generally easy to take and typically do not cause significant laboratory abnormalities. Most people with HIV achieve and maintain viral suppression and have improvement in CD4 count within 1 year after starting ART. Table 3 provides general guidance on the frequency of laboratory monitoring before initiation of and throughout treatment with ART. However, more frequent monitoring of selected tests may be needed as clinically indicated, based on issues such as responses to therapy, underlying medical conditions, drug-related adverse effects, engagement in care, and adherence to therapy. ART is recommended for all people with HIV **(AI);** Table 4 provides guidance for laboratory monitoring in the rare occasions when ART initiation is deferred.

Table 3. Laboratory Testing Schedule Before and After Antiretroviral Therapy Initiation[a]

This table provides general guidance for laboratory monitoring for people with HIV before and after antiretroviral therapy (ART) initiation. Clinicians should use their clinical judgment to determine the monitoring frequency for an individual person based on clinical needs. This schedule is not intended to be a guide on how often people with HIV should undergo clinical evaluation, as some individuals may need to be seen more frequently to accomplish other aspects of clinical care. Please refer to Table 4 for laboratory monitoring guidance if ART initiation is deferred.

Laboratory Test	Timepoint or Frequency of Testing							
	Entry Into Care	ART Initiation[b] or Modification	After ART Initiation or Modification	Every 3–4 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
HIV Antigen/ Antibody Test	✓ If HIV diagnosis not confirmed							
HIV Viral Load	✓	✓	✓[c] At 4–8 weeks	✓[d]	✓[d]		✓	✓
CD4 Count	✓	✓	✓ 3 months (after ART initiation only)	✓[e] If CD4 count is <300 cells/mm^3	✓ During the First 1–2 Years on ART and With Viral Suppression, if CD4 Count Is ≥300 Cells/mm^3: • Every 6 months After 1–2 Years on ART With Consistently Suppressed Viral Load and CD4 Count ≥300 Cells/mm^3: • Optional unless clinically indicated		✓ Monitor CD4 count every 3–6 months.	✓

Table 3. Laboratory Testing Schedule Before and After Antiretroviral Therapy Initiation

Laboratory Test	Timepoint or Frequency of Testing							
	Entry Into Care	ART Initiation[b] or Modification	After ART Initiation or Modification	Every 3–4 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
Genotypic Resistance Testing (PR/RT Genes)[f]	✓	✓					✓	✓
Genotypic Resistance Testing (Integrase Genes)[f]	✓ If transmitted INSTI resistance is suspected or if there is a history of CAB-LA use for PrEP or INSTI use for PEP	✓ If transmitted INSTI resistance is suspected or if there is a history of INSTI use					✓ If there is a history of INSTI use for treatment or prevention	✓
Tropism Testing		✓ If considering a CCR5 antagonist					✓ If considering a CCR5 antagonist, or upon virologic failure on a CCR5 antagonist	✓
HLA-B*5701 Testing		✓ If considering ABC (perform once; keep result in health record)						

Table 3. Laboratory Testing Schedule Before and After Antiretroviral Therapy Initiation

Laboratory Test	Timepoint or Frequency of Testing							
	Entry Into Care	ART Initiation[b] or Modification	After ART Initiation or Modification	Every 3–4 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)[g,h,i] Also see Hepatitis B Virus/HIV Coinfection	✓	✓ In people not immune to HBV, repeat testing if switching to a regimen that does not contain TAF or TDF.						✓ Before starting HCV DAA In people not immune to HBV and at high risk for HBV,[j] periodic testing may be considered.
Hepatitis C Screening (HCV antibody or, if indicated, HCV RNA)[k]	✓					✓ Repeat HCV screening for at-risk people.[j]		✓
Basic Metabolic Panel[l,m]	✓	✓	✓ At 4–8 weeks For people with preexisting conditions or at risk of laboratory changes after ART initiation		✓ Every 6–12 months			✓

Table 3. Laboratory Testing Schedule Before and After Antiretroviral Therapy Initiation

Laboratory Test	Timepoint or Frequency of Testing							
	Entry Into Care	ART Initiation[b] or Modification	After ART Initiation or Modification	Every 3–4 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
ALT, AST, Total Bilirubin	✓	✓	✓ At 4–8 weeks For people with preexisting conditions, at risk for laboratory changes after ART initiation, or with HBV coinfection		✓ Every 6–12 months			✓
CBC With Differential[n]	✓	✓		✓ When monitoring CD4 count (if required by lab)	✓ When monitoring CD4 count (if required by lab)	✓ When no longer monitoring CD4 count		✓
Lipid Profile[o]	✓	✓	✓ At 3–6 months once viral suppression is reached			✓ If aged ≥40 years or on a statin (Every 1–3 years if aged <40 years **and** not on a statin)		✓ If there are changes in CV risk factors[p]

Table 3. Laboratory Testing Schedule Before and After Antiretroviral Therapy Initiation

Laboratory Test	Timepoint or Frequency of Testing							
	Entry Into Care	ART Initiation[b] or Modification	After ART Initiation or Modification	Every 3–4 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
Random or Fasting Glucose[q]	✓	✓						✓
Urinalysis[m,r]	✓							✓ e.g., in people with CKD or DM
Pregnancy Test[s]	✓	✓ For ART initiation; for modification only if clinically indicated						✓

[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 Providers Who Care for Persons With HIV for other laboratory tests generally recommended for primary health care maintenance of HIV people.[1]

[b] If ART is initiated soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

[c] 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.

[d] For people on ART, viral load is typically 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 people with consistently suppressed viral load and stable immunologic status for more than 1 year, monitoring can be extended to 6-month intervals.

[e] After 1–2 years of consistently suppressed HIV RNA, less frequent monitoring (e.g., every 6 months) may be considered.

[f] 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 may have a history of INSTI use as PrEP, PEP, or treatment, or a person presents with viremia while on an INSTI, providers also should test for resistance mutations in the integrase gene. In people who are ARV-naive and 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 people 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 used in constructing a new regimen.

Table 3. Laboratory Testing Schedule Before and After Antiretroviral Therapy Initiation

[g] If a person 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).

[h] 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]

[i] Most people 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 person may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If the test is negative, the person 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]

[j] 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 HBV or HCV infection.

[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 people with elevated ALT may need HCV RNA testing.

[l] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose, and Cr-based eGFR. Serum P should be monitored in people with CKD who are on TDF-containing regimens.[3]

[m] Consult the HIVMA/IDSA's Clinical Practice Guideline for the Management of Chronic Kidney Disease in People Infected With HIV for recommendations on managing people with renal disease.[3] More frequent monitoring may be indicated for people with evidence of kidney disease (e.g., proteinuria, decreased glomerular function) or increased risk of renal insufficiency (e.g., people with diabetes, hypertension).

[n] 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).

[o] If random lipids are abnormal, fasting lipids should be obtained. Consult the American College of Cardiology/American Heart Association/Multisociety Dyslipidemia Guideline for diagnosis and management of people with dyslipidemia.[4]

[p] Changes in CV risk factors such as new diagnosis of hypertension, weight gain, or new medications (including ART) that may raise lipid levels or overall CV risk.

[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 women of reproductive 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; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; P = phosphorus; PEP = post-exposure prophylaxis; PR = protease; PrEP = pre-exposure prophylaxis; RT = reverse transcriptase; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TMP-SMX = trimethoprim-sulfamethoxazole

Table 4. Laboratory Monitoring If ART Is Deferred

Antiretroviral therapy (ART) is recommended for all people with HIV **(AI).** People with HIV should be advised to begin ART as soon as feasible to reduce morbidity and mortality and to prevent transmission of HIV to others. This table provides guidance for laboratory monitoring in the rare occasions when ART initiation is deferred.

Laboratory Test	Initial Assessment	Monitoring Frequency If ART Is Deferred	Comments
CD4 Count	✓	Every 3–6 months	To assess for urgency of ART initiation and the need for OI prophylaxis
HIV Viral Load	✓	Every 3–6 months	
Genotypic Resistance Testing (PR/RT +/- integrase gene) See Drug Resistance Testing for more information.	✓		Repeat genotypic resistance testing at the time of ART initiation is optional.
Hepatitis B Serology (HBsAb, HBsAg, HBcAb) See Hepatitis B in the Adult OI Guidelines for more detailed guidance.	✓	Clinically indicated	Before starting HCV DAA If HBsAg Positive: • ART with HBV-active drugs that include TAF or TDF should be initiated. If Not Immune at Baseline: • Repeat after vaccination or before starting an NRTI-sparing (or limited) ART regimen.
Hepatitis C Screening (HCV antibody, or, if indicated, HCV RNA)	✓	Every 12 months for at-risk people, or if clinically indicated	
Basic Metabolic Panel	✓	Every 6–12 months or if clinically indicated	
ALT, AST, Total Bilirubin	✓	Every 6–12 months or if clinically indicated	
CBC With Differential	✓	When monitoring CD4 count or if clinically indicated	
Pregnancy Test (when pregnancy is possible)	✓	If clinically indicated	ART should be initiated as soon as possible after confirming pregnancy to prevent perinatal HIV transmission.

Key: ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; CBC = complete blood count; CD4 = CD4 T lymphocyte; DAA = direct-acting antiviral; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; PR = protease; RT = reverse transcriptase; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring

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HIV RNA (viral load) and CD4 T lymphocyte (CD4) cell 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 person'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.[1-4] The key goal of ART is to achieve and maintain durable viral suppression. Thus, an important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. The use of viral load testing to confirm the attainment and maintenance of viral suppression is instrumental in the operationalization of Undetectable = Untransmittable (or U=U)/Treatment as Prevention (see the Antiretroviral Therapy to Prevent Sexual Transmission of HIV [Treatment as Prevention] section).

It should be noted that commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in people with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see the HIV-2 Infection section.

CD4 count provides information on the overall immune function of a person with HIV. Measurement of CD4 count at entry into care and **before** initiation of ART is particularly useful in establishing the need to initiate opportunistic infection (OI) prophylaxis. Monitoring **after** initiation of ART is important for assessing immunologic response and establishing the need to discontinue OI prophylaxis.

The management of people with HIV has changed substantially with the availability of newer, more potent, easier-to-use, and less toxic antiretroviral (ARV) drugs. ART is recommended for all people with HIV regardless of their viral load or CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). Because almost all people with HIV in care now receive ART and achieve good immunologic responses, the rationale for frequent CD4 count monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed below.

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 people with HIV at entry into care **(AI),** at initiation of therapy (if treatment is delayed) **(AI),** and on a regular basis thereafter. For those people in whom therapy is delayed, repeat viral load testing is recommended approximately every 3 to 6 months **(BIII),** aligning with CD4 count testing. Repeating viral load testing at these intervals provides an opportunity for discussions about the benefits of ART, both for the treatment of HIV and prevention of HIV transmission. Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because some ARV drugs or regimens have been associated with poorer responses in people with high baseline viral load (see the What to Start section).

Several systematic reviews of data from clinical trials involving thousands of participants in the early era of potent ART have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-4] Thus, viral load testing is an established surrogate marker for treatment response. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold 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 people 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. Several studies showed an increased risk of subsequent failure, drug resistance, morbidity, and mortality at this level of viremia[6-12]; however, the association was not observed in other studies.[10,11,13-17] These guidelines now define virologic failure as the inability to achieve or maintain suppression of viral replication to HIV RNA levels of <200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[18] (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 people. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART:** Plasma viral load should be measured when ART is initiated **(AI)** and within 4 to 8 weeks after treatment initiation **(AIII).** The purpose of these measurements is to confirm an adequate virologic response to ART, indicating appropriate regimen selection and individual adherence to therapy. Repeat viral load measurement should be performed every 4 to 8 weeks until the level falls below the assay's limit of detection **(BIII).**
- **In people with viral suppression, with ART modification because of regimen simplification or drug toxicity:** 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 people 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 people 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 people 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 every 4 to 8 weeks 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 people 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 individual adherence to prescribed medications, suboptimal drug exposure, or drug interactions—should be assessed. People 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 people with HIV. Low pre-treatment CD4 count is the strongest predictor of disease progression and mortality according to findings from clinical trials and cohort studies.[4,19] 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 three percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) **is not recommended (BIII)** because it has not been proven to be clinically useful and is more expensive than monitoring CD4 count alone.

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all people with HIV 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)[20] and the urgency to initiate ART **(AI),** even though ART is recommended for all people with HIV, regardless of CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). Although most OIs occur in people with CD4 counts <200 cells/mm^3, some OIs can occur in people with higher CD4 counts.[21]

Use of CD4 Count for Monitoring Response to ART

The CD4 count is used to assess a person'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).[20] For most people, 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.[22] People who initiate therapy with a low CD4 count[23,24] or at an older age[25] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

ART is recommended for all people with HIV. For people with HIV and pre-treatment CD4 count <300 cells/mm^3, repeating CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII).** This repeat measurement is most important in people who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these individuals, 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. After ART initiation, CD4 count should be repeated every 3 to 4 months for the first 1 to 2 years of suppressive ART for those with CD4 counts <300 cells/mm^3 **(BII)** and every 6 months if CD4 count is ≥300 cells/mm^3 with viral suppression **(BIII).** After 1 to 2 years of suppressive ART, reducing CD4 count monitoring to every 6 months may be considered for some people whose CD4 counts remain at <300 cells/mm^3 **(BIII);** for those with CD4 counts ≥300 cells/mm^3, CD4 count monitoring is optional unless clinically indicated **(BIII).**

The CD4 count response to ART varies widely, but a poor CD4 response in a person with viral suppression is rarely an indication for modifying an ARV regimen (see the Suboptimal CD4 Recovery section). In people with consistently suppressed viral loads who have already experienced ART-related immune reconstitution (i.e., CD4 count ≥300 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 people with viral suppression and CD4 counts >300 cells/mm^3.[26] Similarly, the ARTEMIS trial found that CD4 count monitoring had no clinical benefit in people who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[27] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in people on suppressive ART who have CD4 counts between 100 cells/mm^3 and 200 cells/mm^3.[28] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed people and may be associated with adverse clinical outcomes, such as cardiovascular disease, malignancy, and death.[29,30]

An analysis of costs associated with CD4 count monitoring in the United States estimated that reducing CD4 count monitoring in treated people from every 6 months to every 12 months could result in annual savings of approximately $10 million.[31]

CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a person'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 people who do not maintain viral suppression while on ART, CD4 count monitoring should be done every 3 to 6 months **(AIII).**

In people who remain untreated for whatever reason, CD4 count should be monitored every 3 to 6 months to monitor for disease progression and assess the urgency of ART initiation and the need for OI prophylaxis **(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[32,33] or coinfection with human T-lymphotropic virus type I[34] may cause misleadingly elevated CD4 counts. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a person's immune function.[35]

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Drug-Resistance Testing

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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 women 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 women 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 woman and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant women 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.
For pregnant women 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.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
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.
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.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
In Pregnant Women With HIV Genotypic resistance testing is recommended for all pregnant women before initial ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI).**	The goals of ART in pregnant women with HIV are to achieve maximal viral suppression for treatment of HIV in the pregnant woman 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 an 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

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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

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Antiretroviral therapy (ART) reduces HIV-related morbidity and mortality at all clinical stages of HIV[1-5] and reduces sexual and perinatal HIV transmission to others.[6-11] In addition, maximal and durable viral suppression preserves or improves CD4 T lymphocyte (CD4) cell count, prevents the selection and archival of drug-resistance mutations, and prevents sexual and perinatal transmission of HIV, all of which are important treatment goals. Early HIV diagnosis and ART initiation provide the best opportunity to maximize the benefits of ART.[3,12-14] Data show that with contemporary ART, viral suppression has improved, and adverse effects leading to treatment discontinuation have declined over time.[12] ART-mediated viral suppression may also decrease inflammation and immune activation, thought to contribute to higher rates of cardiovascular and other end-organ disease reported in cohorts with HIV (see Initiation of Antiretroviral Therapy and Immune Activation and Inflammation Among People With HIV Receiving Antiretroviral Therapy). Despite these benefits, eradication of HIV infection cannot be achieved with currently available antiretroviral (ARV) drugs. Treatment interruption has been associated with rebound viremia, worsening of immune function, and increased morbidity and mortality.[15] Thus, once initiated, ART should be continued for life, with the following key treatment goals:

- Maximally and durably suppress plasma HIV RNA (viral load)
- Restore, preserve, and improve immunologic function
- Reduce HIV-associated morbidity and prolong the duration and quality of survival
- Prevent HIV transmission

Achieving viral suppression requires the use of combination ARV regimens that generally include two or three active drugs from two or more drug classes. Certain baseline characteristics and results from drug-resistance testing should guide design of the specific regimen (see What to Start). With the currently available ARV drugs, including long-acting injectable drugs, durable viral suppression can be achieved by >90% of people with HIV who adhere to their prescribed regimens.[16-18] If viral suppression is not achieved or maintained despite an assessment of adherence and other structural barriers to care, changing to a new regimen should be guided by ART history, prior treatment responses, and current and historic drug-resistance testing (see Virologic Failure).

After initiation of effective ART, viral load typically declines to below the limits of assay detection within the first 8 to 12 weeks of therapy. Predictors of virologic success include the following:

- Earlier stage of HIV disease (higher CD4 count) at ART initiation
- Low baseline viremia
- High potency of the ARV regimen
- Tolerability of the regimen
- Convenience of the regimen
- Excellent ART adherence and engagement in care

Strategies to Achieve Treatment Goals

Selection of Initial Combination Regimen

Several ARV regimens are recommended for use as initial therapy (see What to Start). The recommended regimens have comparable efficacy but with slight variation in pill burden (one or two pills daily), potential for drug interactions and/or side effects, propensity to select for resistance mutations if ART adherence is suboptimal, and appropriateness for use in people with hepatitis B virus coinfection. Regimens should be individualized to enhance adherence and support long-term treatment success. Considerations when selecting an ARV regimen for an individual include comorbidities, such as viral hepatitis; prior use of HIV pre-exposure prophylaxis; possible interactions with concomitant medications; results of pre-treatment genotypic drug-resistance testing; potential adverse effects; and regimen convenience (see Table 7).

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex ARV regimens, individual circumstances (e.g., substance use, mental health conditions, adverse effects), and structural barriers to treatment access, education, or support. Conditions that promote adherence should be maximized before and continue after initiation of ART (see Adherence to the Continuum of Care). For some people with HIV, switching to a simpler or better-tolerated ARV regimen can improve treatment outcomes (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).

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INITIATION OF ANTIRETROVIRAL THERAPY

Updated: September 25, 2025
Reviewed: September 25, 2025

Panel's Recommendations
• The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends antiretroviral therapy (ART) for all people with HIV to reduce morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI).** • The Panel 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 people with HIV **(AII).** • When initiating ART, people with HIV should be counseled on the benefits, lifelong need, and importance of adherence to ART; clinicians should also identify and address barriers to care engagement and ART 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 goals of antiretroviral therapy (ART) are to prevent HIV-associated morbidity and mortality and to prevent transmission of HIV to others. These goals are accomplished by using effective ART to achieve and maintain plasma HIV-1 RNA levels (viral load) below the quantification limits of commercially available assays. Durable viral suppression lowers the risk of both AIDS-defining and other HIV-related complications, improves immune function and overall health, and allows people with HIV to live a lifespan approaching that of people without HIV.[1,2] High plasma viral load is a major risk factor for HIV transmission; effective ART suppresses viremia and, consequently, substantially reduces the risk of sexual[3-7] and perinatal HIV transmission.[8,9] Modeling studies and ecological studies of populations with high ART uptake and high viral suppression rates suggest that expanded use of ART lowers the incidence of HIV and, eventually, the prevalence of HIV on a community or population level.[10-12]

Early clinical trials of combination ART focused on people with advanced HIV and low CD4 T lymphocyte (CD4) cell counts.[13-15] Consequently, treatment guidelines at that time recommended the initiation of ART based on CD4 count thresholds or the development of AIDS-defining conditions. The benefits of ART for people with high CD4 counts were unclear, along with concerns about the toxicities of some antiretroviral (ARV) drugs. However, two large randomized controlled trials, START[16] and TEMPRANO[17], both published in 2015, addressed the optimal time to initiate ART. Both studies demonstrated reductions in morbidity and mortality among people with HIV who had CD4 counts >500 cells/mm^3 and who initiated ART immediately when compared with people who delayed initiation of ART.

Deferring ART until CD4 counts decline puts people 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, some 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,[18,19] and they have a shorter life expectancy than those who initiated therapy at higher CD4 count thresholds.[18-20]

Fundamental to the recommendation for earlier initiation of ART is the assumption that HIV will be diagnosed early in the course of the disease. The Centers for Disease Control and Prevention (CDC) recommends HIV screening to be performed for all people aged 13 to 64 years, including during pregnancy, using an opt-out screening approach.[21] More frequent HIV screening is recommended for certain populations with higher HIV prevalence.[22] The U.S. Preventive Services Task Force (USPSTF) also recommends HIV testing for people aged 15 to 65 years and for all pregnant women. This recommendation has been designated a Grade A recommendation by the USPSTF, meaning that third-party payers should cover this service without cost to patients.[23] HIV testing should also be performed for people younger than 15 and older than 65 years of age when indicated or requested.

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.[24] Delayed diagnosis of HIV has been reported more often in people who inject drugs, people who live in rural communities, older adults, and among Black and Hispanic persons.[25-27] Many people with HIV access health care years before their HIV diagnosis but are not offered HIV testing.[28]

To ensure that the current treatment guidelines have maximum impact, routine HIV screening per current CDC or USPSTF recommendations is essential.[23,29] Early diagnosis also has clinical and economic benefits, including prolonging life, improving the quality of life, and decreasing the costs related to the management of AIDS and its comorbidities.[30,31] Additionally, HIV screening is a key step in the Ending the HIV Epidemic initiative to prevent the transmission of HIV to others.[32] It is critical that everyone who receives an HIV diagnosis be educated about HIV disease; initiated on ART; and linked to care for full evaluation, follow-up, and management as soon as possible. In order for people 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 engagement in care and full ART adherence (see Adherence to the Continuum of Care and Treatment as Prevention).

Initiating Antiretroviral Therapy

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends ART for all people 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).** Clinicians should refer to What to Start for guidance on ART regimen selection for all adults and adolescents with HIV, including those who received pre-exposure prophylaxis (PrEP) before HIV diagnosis; the Perinatal Guidelines provide guidance on ART regimen selection during pregnancy. When initiating ART, people with HIV should be counseled on the benefits, lifelong need, and importance of adherence to ART; clinicians should also identify and address barriers to care engagement and ART adherence **(AIII).** People with HIV should also understand that the 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 as soon as possible is particularly important for people with AIDS-defining conditions, those with acute or recent HIV infection, and during pregnancy. Delaying therapy in these subpopulations may increase risks for morbidity, mortality, and HIV transmission. Laboratory Testing for Initial Assessment and Monitoring of People With HIV Receiving Antiretroviral Therapy provides recommendations for baseline and follow-up laboratory monitoring for people starting ART.

Early (Acute/Recent) HIV Infection

The term "early HIV" refers to both acute and recent infection. "Acute HIV" occurs soon after transmission (onset of symptoms typically within 2–4 weeks after infection) and is characterized by the presence of HIV RNA alone or with positive p24 antigen and nonreactive or indeterminate HIV antibody results on the confirmatory immunoassay. "Recent HIV" refers to the first 6 months after infection, during which anti-HIV antibodies and HIV RNA become detectable.[33,34] Detailed discussion on the diagnosis of acute HIV can be found in Early (Acute and Recent) HIV Infection.

Early HIV is considered a period of high infectivity,[35] and early ART substantially reduces the risk of HIV transmission.[4-7] Additionally, clinical trial data indicate that individuals who are treated during early HIV may experience immunologic and virologic benefits.[36-41] Therefore, ART should be initiated as soon as possible after a positive qualitative test result or a quantitative HIV RNA test result **(AII).** Before starting ART, and without delaying its initiation, a blood sample should be sent for genotypic resistance testing (see Drug Resistance Testing and What to Start). Same-day or rapid ART initiation in people with acute HIV has been shown to be safe, acceptable, and effective.[42] When initiating ART, clinicians should identify and address barriers to ART adherence and engagement in care for each person with HIV (see Adherence to the Continuum of Care).

To verify the diagnosis of acute HIV, a new blood specimen should be collected for a confirmatory HIV antibody test and a quantitative plasma HIV RNA test. Given the sensitivity of current HIV RNA assays,[43] 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. If acute HIV is highly suspected, ART should be initiated without delay while awaiting confirmation of diagnosis[44]; if the pending test results later rule out HIV infection, then ART for the treatment of HIV should be discontinued. People who tested negative but remain at risk of sexual HIV transmission should be offered ARV PrEP per recommendations from the CDC.

Some individuals with early HIV may decline ART initially. 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.

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

ART initiation on the same day of HIV diagnosis in the outpatient setting may be used as a strategy to increase ART uptake and engagement in care, to accelerate the time to ART-mediated viral suppression, and, consequently, to reduce the potential for HIV transmission. Benefits of rapid ART initiation are supported by randomized controlled trials that were performed in resource-limited settings outside of the United States[45-47] and observational trials in the United States that included both immediate initiation of ART (on the day of diagnosis)[48-50] and rapid ART initiation (within days or weeks of diagnosis).[50,51] Two randomized trials were performed in South Africa (n = 377)[45] and Haiti (n = 703).[46] In these trials, same-day ART initiation increased the proportion of participants who had suppressed viral loads about a year after HIV diagnosis compared with those who initiated ART between 3 weeks and 3 months after diagnosis. In addition, these studies demonstrated that rapid ART initiation can be feasible and beneficial in resource-limited settings. 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 resulted in ART initiation on the day of diagnosis for more than half of the patients and a median time from ART initiation to viral suppression (defined as <200 copies/mL) of 41 days. Over a median follow-up of 1.1 years (range 0–3.9 years), 92.1% of patients achieved virologic suppression. In the

RAPID study, a substantial proportion of participants had a major substance use disorder (51.4%), a major mental health disorder (48.1%), or unstable housing (30.6%).[49]

It should be emphasized that ART initiation on the same day of HIV diagnosis can be resource intensive. 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.[49] While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, facilitating rapid ART initiation may improve treatment outcomes. 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 **(AII).** The rating for this recommendation reflects the fact that randomized trials have only been conducted in low-resource countries, while evidence for benefit in the United States is based on observational studies.

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 are some important factors to consider when initiating ART in these situations.

- **When no effective therapy exists for the treatment of the OI (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy):** In these situations, ART is the only treatment that can improve immune function and clinical outcomes. ART should be initiated without delay.
- **Concerns about immune reconstitution inflammatory syndrome (IRIS):** For some OIs, such as cryptococcal and tuberculosis (TB) meningitis, immediate ART initiation may increase the risk of serious IRIS. A short delay before initiating ART may be warranted.[52-55] After ART initiation, the patient should be closely monitored for signs and symptoms associated with IRIS.
- **Nonmeningeal TB:** In these patients, initiating ART during treatment for TB confers a significant survival advantage[56-60]; therefore, ART should be initiated as recommended in Tuberculosis/HIV Coinfection.
- **For people 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.[61]
- **For people with other OIs:** After starting treatment for the OI, ART should be initiated as soon as feasible to improve immune function.
- **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,[62] ART-mediated viral suppression is associated with longer survival among individuals undergoing treatment for AIDS-related lymphoma.[63]

Importantly, drug interactions should be considered when selecting ART, as there is the potential for significant interactions between some ARV drugs (particularly ritonavir- or cobicistat-boosted regimens) and drugs for treatment of OIs (particularly with rifamycins and azole antifungal drugs) and chemotherapy drugs.

Antiretroviral Therapy Initiation in Hospitalized People With HIV

Some people receive their first HIV diagnosis while hospitalized for HIV-related or unrelated conditions.[64] The test-and-treat concept of initiating ART has been successful in the outpatient setting as described above; however, newly diagnosed people with HIV who are hospitalized seldom start ART before hospital discharge.[65] Some concerns about initiating ART during hospitalization include the potential for drug–drug interactions or ART-related adverse effects that may complicate management of the acute condition that prompted hospitalization, the risk of paradoxical or unmasking IRIS in the context of OIs, and limited HIV care experience among hospital staff. Additionally, securing ART prescription coverage for a person with newly diagnosed HIV requires a multidisciplinary approach, including coordination with social workers/case managers to navigate through some complex insurance/patient assistance programs. As a result, some clinicians prefer to leave this task to the primary HIV clinic.

Although receiving an HIV diagnosis during an acute illness can be overwhelming, several reasons make this an opportune time to initiate ART. For example, being hospitalized allows more time for the person with HIV to receive education and ask questions about HIV and treatment goals and to receive ART-related counseling. Upon patient approval, having family or caregivers participate in these discussions will allow them to assist with adherence to ART (and concomitant medications) and clinic follow-up after discharge. Administering the first doses of ART during hospitalization allows clinicians to assess ART tolerance while under observation. Using a multidisciplinary team approach (e.g., HIV specialists, pharmacists, social workers) during the hospital stay to assist with ART initiation can facilitate transition to outpatient care. Clinical pharmacists can assess for potential drug–drug and drug–nutrient interactions and provide counseling on ART and adherence. Social workers/patient navigators can assist with exploring options for outpatient ARV coverage and facilitate linkage to HIV primary care. A multicenter study that enrolled hospitalized people with HIV from 2012 to 2014 demonstrated that starting ART in hospitalized patients who had a recent history of substance use was associated with shorter time to linkage to their first HIV clinical appointment after discharge and more clinic visits in the first 12 months after ART initiation than those who were not started on ART before discharge; however, no difference was observed in the rate of viral suppression and retention in care over 12 months.[66]

Certain situations, such as in the setting of TB meningitis or cryptococcal meningitis, may warrant a short delay in ART initiation due to concerns of severe consequences related to paradoxical IRIS; however, in most other situations, the benefits of starting ART during hospitalization outweigh the concerns listed above. Therefore, the Panel recommends initiating ART during hospitalization whenever possible **(BIII).**

Before starting ART, and without delaying its initiation, a blood sample should be sent for genotypic resistance testing (see Drug Resistance Testing and What to Start). If the resistance testing results are not available before hospital discharge, they should be forwarded to the outpatient HIV provider as soon as they become available. If ART is initiated before hospital discharge, clinicians should coordinate with their multidisciplinary team to ensure sufficient ART supply (e.g., at least 2–4 weeks' supply) is available until the outpatient clinic appointment. See Adherence to the Continuum of Care for more discussions on the transition of care between different health care settings.

Evidence Supporting the Benefits of Antiretroviral Therapy in Preventing Morbidity and Mortality

Randomized Controlled Trials of Early Versus Deferred Antiretroviral Therapy

Two large randomized controlled trials, START and TEMPRANO, published in 2015, provided 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, multinational, randomized controlled clinical trial designed to evaluate the role of early ART initiation in asymptomatic adults with high CD4 counts in reducing AIDS-defining illnesses, serious non-AIDS events, or death. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm^3 were randomized to initiate ART at randomization (immediate 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 arm).

The study enrolled 4,685 participants. Initial results were unblinded early (after a mean follow-up of 3 years) because of the superiority of the immediate ART strategy. 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) in the immediate ART arm 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 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 immediate ART was consistent across all participant subgroups, including sex, age, plasma HIV RNA levels, and country income level. 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. In addition to AIDS-related events, early ART initiation also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61).[16,67]

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/mm^3 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, early ART reduced the rate of primary events compared with deferred ART, with an HR of 0.56 (95% CI, 0.33–0.94).[17]

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. Guidelines around the world now recommend starting ART irrespective of CD4 count at the time or soon after HIV diagnosis.

Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A randomized clinical trial[4] and several large observational cohort studies[5-7] 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 people 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 partners **(AII).** People with HIV 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. Clinicians should also discuss with these individuals the potential harm of non-adherence to ART, including that it can lead to viremia, which may affect their own health, lead to drug resistance, and potentially transmission to sexual partners.

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%–30% to 0.1%–0.5%.[8,9] ART is thus recommended during all pregnancies in the context of HIV, for both maternal health and for the prevention of HIV transmission to the newborn. In ART-naive pregnant women, ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy. HIV testing should be performed upon confirmation of pregnancy, with testing repeated throughout pregnancy as needed for those at risk of HIV acquisition (see Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal 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 people who fully adhere to their regimens. Most of the recommended regimens have a low pill burden (one or two pills once daily) and are well tolerated. People with HIV should be assessed for coexisting medical conditions and medications that may influence the selection of ART regimens or require dose adjustments or additional monitoring (see What to Start). Once started on treatment, patients must continue ART indefinitely, although future switches to alternative ART regimens may occur due to adverse events, drug–drug or drug–food interactions, cost, regimen simplification, or other reasons.

Optimizing Adherence, Antiretroviral Therapy Access, and Care Engagement

The key to successfully maintaining viral suppression is continuous access to ART and full 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.[68-70] 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 psychiatric disorders, neurocognitive impairment, substance use disorder, unstable housing, patient concerns about side effects, difficulty remembering, demanding or irregular daily routines, experiences of HIV-related stigma, and ongoing adjustment to HIV diagnosis. Clinicians should identify areas in which 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 people with HIV maintains plasma viral load below the level of quantification for years without ART. These individuals are often referred to as elite HIV controllers.[71,72] Data on the role of ART and the optimal management of elite controllers are sparse, and clinicians should engage in shared decision-making with the elite controller.

Despite the absence of detectable viremia, ongoing HIV replication occurs even in HIV elite controllers. In addition, even with normal CD4 counts, elite controllers show evidence of abnormally high immune activation, chronic inflammation, immune aging, and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS–related diseases.[71,73-77] One observational multisite study in the United States suggested that elite controllers not receiving ART are hospitalized more often for cardiovascular and psychiatric disease than well-controlled patients on ART.[78] A subsequent observational study did not show an increase in the incidence of hospitalization, but the study population was younger and had a lower incidence of hepatitis C virus (HCV) coinfection than that of the previous study.[79] In additional cohort studies of HIV elite controllers, loss of viral control, older age, and HCV coinfection were independently associated with a higher incidence of non-AIDS–defining events.[79-82]

Elite controllers with preserved CD4 counts appear to experience a decline in immune activation and the size of the HIV reservoir after ART initiation, suggesting that treatment may be beneficial.[77,83] Whether this potential immunologic benefit of ART in elite controllers outweighs the potential risks of ART-associated adverse effects is unclear.[77] Unfortunately, given the very low prevalence of elite controllers, it is unlikely that randomized controlled trials will be able to address this question.[84] Nevertheless, there is a clear rationale for prescribing ART to some elite controllers even in the absence of detectable plasma viral load.

Based on discussions above, the Panel strongly recommends ART for elite controllers with evidence of HIV-related complications, declining CD4 counts, intermittent detectable viral load, or comorbidities (e.g., cardiovascular disease, cancer, hepatitis B virus/HCV coinfection), or for those who are pregnant **(AIII).** The Panel also recommends initiation of ART for all other HIV elite controllers **(BII).** If ART is deferred, elite controllers should be followed closely, as some may experience CD4 count decline, loss of viral control, or complications related to HIV infection.

Adolescents and Young Adults With HIV

Neither the START trial nor the TEMPRANO trial included adolescents aged <18 years. The Panel's recommendation to initiate ART in all people with HIV is extrapolated to adolescents based on the expectation that they will derive benefits from early ART initiation similar to those observed in adults. However, adolescence is marked by socioemotional, cognitive, and developmental changes that can increase the risk of treatment nonengagement. Compared with adults, adolescents have demonstrated significantly lower levels of ART adherence and viral suppression, as well as higher rates of viral rebound following initial viral suppression.[85] In recent years, more adolescents have been prescribed once-daily regimens, which has increased the rate of viral suppression in this population.[86] 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 and young adults may not be immediately ready to initiate therapy, clinicians should offer ART, preferably fixed-dose, once-daily regimens with a high barrier to drug resistance, alongside effective interventions to assess and address existing and potential barriers to care and adherence. To optimize the benefits of ART for youths, multidisciplinary care teams should individualize psychosocial and adherence support to adolescents and young adults (see Adolescents and Young Adults With HIV).[87]

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ANTIRETROVIRAL THERAPY TO PREVENT SEXUAL TRANSMISSION OF HIV (TREATMENT AS PREVENTION)

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Reviewed: September 25, 2025

Panel's Recommendations
• All people 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. This concept may be recognized as Undetectable = Untransmittable or U=U **(AII).** • People with HIV who are starting ART should use another form of prevention with sexual partners (e.g., condoms, sexual abstinence, pre-exposure prophylaxis [PrEP] for the sexual partner who is HIV-negative) for at least the first 6 months of ART 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).** • When the viral load is ≥200 copies/mL, at least one additional HIV prevention method (e.g., condoms, sexual abstinence, or PrEP for the HIV-negative partner) is recommended to prevent sexual HIV transmission until resuppression to <200 copies/mL is confirmed **(AIII).** • People with HIV who intend to rely on ART as 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 people with HIV on the importance of ART for their own health as well as its role in preventing sexual HIV transmission **(AIII).** • Providers should inform people with HIV 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 people with HIV who are sexually active 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 people with HIV but has 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 people with HIV need to be aware of the data supporting treatment as prevention (TasP, which may be recognized as Undetectable = Untransmittable or U=U), its implications, and how to operationalize this prevention strategy in clinical practice. For people with HIV who intend to rely on TasP to prevent sexual transmission, providers should make an individualized assessment that considers 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 people 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 a 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 (range <50 to <500 copies/mL).

The first prospective clinical trial designed specifically to address this question was HPTN 052, which randomized people with HIV with CD4 T lymphocyte cell (CD4) count between 350 cells/mm^3 and 550 cells/mm^3 who were in mixed–HIV status relationships (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, in which the partners with HIV were 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 had presumably not yet achieved viral suppression. Four other transmissions occurred after the partner with HIV experienced virologic failure. A number of transmission events occurred that were not phylogenetically linked, indicating acquisition from someone other than the partner enrolled in the study.[11] HPTN 052 was conducted almost exclusively among heterosexual couples who 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 reduce stigma and provide additional motivation for individuals to get tested, enter into and engage in care, initiate and adhere to ART, and ultimately achieve and maintain viral suppression.[15] Although the PARTNER 1, PARTNER 2, and Opposites Attract trials were designed to follow participants in the study as they would 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 and Opposites Attract studies, viral loads were generally assessed every 3 to 6 months during study follow-up, usually during the course of regular HIV care. The Panel recommends a similar frequency for monitoring viral load (every 3–6 months) as in the section of the guidelines **(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 only included the 1,573 heterosexual East African couples in which the partners without HIV were randomized to the placebo arm of the 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 and before documented viral suppression. After the partners with HIV had been taking ART for ≥6 months, no further transmissions were observed.

At this time, the Panel recommends that people with HIV who are starting ART should use another form of prevention with sexual partners (e.g., consistent condom use, sexual abstinence, pre-exposure prophylaxis [PrEP] for sexual partners without HIV) for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented **(AII).** Confirming sustained viral suppression is recommended before assuming that sexual transmission of HIV is no longer a risk **(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 oral ARV medications.[17-31] The minimum level of adherence that is required to prevent sexual transmission has not been determined and may vary depending on the ART regimen and the route of administration (orally vs. parenterally). 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 maintaining viral suppression can be a challenge for some people, especially for those who have difficulty accessing ART and other HIV care. The Centers for Disease Control and Prevention (CDC) estimates that during 2023, 76.3% of persons aged 13 years or older with HIV were engaged in clinical care, and only 67.2% had viral loads <200 copies/mL at their most recent assessment.[32] 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, typically no more than 5% to 10% of people on ART experience loss of viral suppression.[33-35]

Adherence can be especially challenging for certain groups, such as adolescents and young adults, people with unstable housing, people with active substance use disorder(s), and people who are justice-involved. Recommendations to help manage and maximize ART adherence can be found in Adolescents and Young Adults With HIV. 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.

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).** People with HIV should be informed that transmission is possible during periods of poor adherence or treatment interruption **(AIII).**

Managing Transient Viremia, or "Blips"

Occasionally, some people who are highly adherent 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 some earlier ART regimens, up to 16% of persons per year who are adherent to ART may experience a blip.[36-39] Most blips likely represent normal biological fluctuation (i.e., variation around a mean undetectable viral load) or laboratory artifact and not inadequate adherence.[40-42] Persistent viremia ≥200 copies/mL has been associated with increasing risk of virologic failure[36,39,43-46] that, in the context of TasP, can lead to increased risk of sexual transmission of HIV.[10] The PARTNER and Opposites Attract studies 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 >50 copies/mL 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 any time the viral load is ≥200 copies/mL, people with HIV and their sexual partners should be counseled to 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 and sustained **(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 person achieves resuppression to <200 copies/mL after a detectable viral load ≥200 copies/mL (e.g., blips, viremia), or when a person with a viral load <200 copies/mL switches regimens (e.g., for regimen simplification or to avoid certain side effects), providers should follow situation-specific viral load monitoring recommendations **(AIII)** (see Plasma HIV-1 RNA [Viral Load] and CD4 Count Monitoring). 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 HIV transmissions 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 a 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 the CDC's Sexually Transmitted Infections 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 in preventing transmission from blood exposure 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

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Introduction

More than 30 antiretroviral (ARV) drugs in nine mechanistic classes have been U.S. Food and Drug Administration (FDA)–approved for treatment of HIV. 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 (no longer available), 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 select 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. For more information, see Principles of Antiretroviral Therapy.

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) now recommends initial ARV regimens based on an oral second-generation INSTI plus one or two NRTIs for most people with HIV **(**see **Table 6a** below**).** When INSTI resistance is possible, such as after exposure to long-acting injectable cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) and INSTI resistance results are not yet available, a boosted PI in combination with two NRTIs is recommended. The tables below outline the Panel's initial recommended regimens for most people with HIV (**Table 6a**) and for certain clinical scenarios (**Table 6b**).

Table 6a. Recommended Initial Regimens for Most People With HIV

Selection of an ARV regimen 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 select comorbid conditions of the person with HIV. A pregnancy test should be performed in women of childbearing potential, and choice of ART for pregnant women 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)**
- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI),** except for individuals—
  - With HBV coinfection.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

For people who have a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before starting INSTI-based ART. If ART is to be started before results of genotypic testing, the following regimen is recommended:

- DRV/c[c] or DRV/r plus (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: Of regimens listed in Table 6a, 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. 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 Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios). These regimens are listed below.

Type of Regimen	ARV Regimen	Rapid Start	For Certain Clinical Scenarios	Other Considerations
INSTI Plus Two NRTIs	DTG/ABC/3TC **(BI)** (if HLA-B*5701-negative)	No	When concern about renal- or bone-associated AEs precludes the use of TDF or TAF or when DTG/3TC cannot be used	Test for HLA-B*5701 before prescribing ABC; ABC is **contraindicated** if HLA-B*5701-positive. Consider alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known CVD. Do not use in people with HBV unless an HBV-active drug other than 3TC (i.e., entecavir) is also used. Do not use following exposure to CAB-LA unless INSTI genotype shows sensitivity to DTG.
Boosted PI Plus Two NRTIs	(DRV/c[a] or DRV/r) plus (TAF or TDF[b]) plus (FTC or 3TC) **(BI)**	Yes	To avoid an INSTI-based regimen (e.g., suspected or documented INSTI resistance)	Assess for potential RTV- or COBI-related DDIs (see the Liverpool HIV Drug Interaction Checker). Needs to be taken with a meal.
	(DRV/c[a] or DRV/r) plus ABC/3TC **(BII)** (if HLA-B*5701-negative)	No	To avoid an INSTI-based regimen (e.g., with suspected or documented INSTI resistance), *and* When concerns about renal or bone-associated AEs preclude the use of TDF or TAF	Test for HLA-B*5701 before prescribing ABC; do not prescribe if HLA-B*5701-positive. Consider alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known CVD. Do not use in people with HBV unless used with an HBV-active drug other than 3TC (i.e., entecavir). Assess for potential RTV- or COBI-related DDIs. Needs to be taken with a meal.

Table 6b. Initial Antiretroviral Regimens for Certain Clinical Scenarios

Type of Regimen	ARV Regimen	Rapid Start	For Certain Clinical Scenarios	Other Considerations
Boosted PI Plus One NRTI	DRV/r plus (3TC **[BI]** or FTC **[BII]**), *or* DRV/c plus (3TC or FTC) **(BII)**	No	To avoid TFV and ABC in people who are not candidates for DTG/3TC	Do not use if genotypic resistance testing for reverse transcriptase is not yet available. Do not use in people with HBV unless used with an HBV-active drug other than 3TC (i.e., entecavir). Assess for potential RTV- or COBI-related DDIs (see the Liverpool HIV Drug Interaction Checker). Needs to be taken with a meal.
NNRTI Plus Two NRTIs	DOR/TDF/3TC[b] **(BI)** *or* DOR plus TAF/FTC[b] **(BIII)**	No	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	No	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	**Contraindicated** with PPI; space apart from H2 antagonist or antacids. Needs to be taken with a meal.

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-boosted DRV **is not recommended** as part of initial therapy 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.

Table 6b. Initial Antiretroviral Regimens for Certain Clinical Scenarios

[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; ASCVD = atherosclerotic cardiovascular disease; CAB-LA = long-acting cabotegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; CVD = cardiovascular disease; 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 initial ARV 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 the evidence rating **"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) *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 *Initial Antiretroviral Regimens for Certain Clinical Scenarios*. See Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios 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. As such, 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, including Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios and Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy. Appendix A, Tables 3–10, lists characteristics of individual ARV agents for initial therapy (e.g., formulations, dosing recommendations, PK, common adverse effects). Appendix B provides ARV dosing recommendations for people who have renal or hepatic insufficiency. See the Liverpool HIV Drug Interaction Checker for potential drug interactions.

Changes Since the Last Revision of the Guidelines

The Panel has made several important changes since the last revision of these guidelines, as outlined below.

Changes to the Recommended Initial Regimens for Most People With HIV

- The single-tablet regimen (STR) dolutegravir (DTG)/lamivudine (3TC) is now recommended for initial therapy regardless of baseline plasma HIV RNA if there is no evidence of genotypic resistance to 3TC and there is documented absence of chronic hepatitis B virus (HBV) infection (see *Recommended Initial Regimens for Most People With HIV*). This change is based upon the DOLCE study, which showed similar efficacy for DTG/3TC compared with DTG and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or TDF/3TC for initial therapy among people with advanced HIV infection. There was no significant difference between the DTG/3TC arm and the three-drug arm in the subgroup with HIV viral load >500,000 copies/mL.[1]

Changes to Initial Antiretroviral Regimens for Certain Clinical Scenarios

- The two-drug combinations of (darunavir/ritonavir [DRV/r] or darunavir/cobicistat [DRV/c) plus (3TC or FTC) are now recommended two-drug regimens for people with HIV who need to avoid tenofovir (TFV) and abacavir (ABC) and who are not candidates for DTG/3TC. This change is based on the ANDES study showing similar efficacy in those receiving DRV/r plus 3TC compared with those receiving DRV/r plus TDF/FTC or TDF/3TC.[2]

Other Additions

- DTG/3TC is now classified as an *Alternative* regimen in pregnancy. See the Perinatal Guidelines for more information.

- Doravirine (DOR) is noted to have a distinct resistance pathway and potentially higher barrier to resistance compared with other NNRTIs, although not comparable to that of boosted PIs or second-generation INSTIs.
- Refer to the Liverpool HIV Drug Interaction Checker for drug–drug interaction guidance between ARV drugs and concomitant medications.

Selecting an Initial Antiretroviral Regimen

The goal of antiretroviral therapy (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 Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios 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 tenofovir alafenamide (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 include 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: HBV, hepatitis C virus, tuberculosis
- Pregnancy and potential for pregnancy: See below in General Considerations for Women 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). ABC **is contraindicated** in those who are HLA-B*5701 positive. See Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios 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 and the Liverpool HIV Drug Interaction Checker)
- 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 or acquired 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.[3]
- 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.[4] 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.[5] 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 darunavir (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. This recommendation is based largely on the fact that although INSTI resistance could occur in the setting of INSTI-based PEP failure, it is likely to be uncommon. In addition, transmitted INSTI resistance remains low in the United States.

General Considerations for Women of Reproductive Potential Initiating Antiretroviral Therapy

- A pregnancy test should be performed before initiating ART.
- Clinicians should discuss intentions regarding pregnancy with all women 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 bictegravir [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 Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios and Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy).

INSTI-Based Regimens

The Panel's *Recommended Initial Regimens for Most People With HIV* include one of two INSTIs: BIC coformulated with TAF/FTC **(AI);** or DTG plus TAF or TDF plus FTC or 3TC **(AI);** or DTG coformulated with 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 are 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.[6-8]

The Panel recommends a two-drug regimen of DTG/3TC for initial therapy in those with documented absence of both transmitted NRTI resistance and chronic HBV infection. Data from two randomized trials showed that, in terms of virologic efficacy, DTG plus 3TC was noninferior to a three-drug regimen of DTG plus TDF/FTC. A third randomized trial demonstrated similar outcomes in patients with advanced HIV infection, as defined by CD4 counts ≤200 cells/mm^3, many of whom had very high viral loads.[1] Moreover, no treatment-emergent resistance was seen in any of these two-drug or three-drug study groups.[9] Based on the need for resistance testing and HBV serology, DTG/3TC is not currently recommended for rapid ARV initiation before the availability of HBV serology and an HIV genotypic test demonstrating sensitivity to NRTIs. Although not *Preferred*, DTG/3TC is recommended as an *Alternative* treatment option for pregnant women with HIV (see the Perinatal Guidelines for more information).

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 raltegravir (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[10-13] and BIC-based regimens.[14-17] Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens with two NRTIs 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 noninferior to DTG-based regimens in clinical trials.[18-20]

Some data suggest 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.[21-28] See Weight Gain in People With Treated HIV for more information.

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 P450 3A4 inhibitor (see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).

PI-Based Regimens

In the setting of HIV acquisition following CAB-LA exposure, a regimen of RTV- or COBI-boosted DRV 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),** or in certain clinical situations when INSTIs must be avoided (e.g., suspected or documented INSTI resistance) **(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.[29-34] COBI-boosted regimens should not be initiated during pregnancy because of inadequate drug levels. Boosted ATV is no longer recommended as initial therapy because of frequent adverse events (e.g., hyperbilirubinemia) and high rates of drug–drug interactions, including with TFV and acid-suppressive therapy.

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 rilpivirine (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 boosted PIs or second-generation INSTIs.

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 noninferior to both efavirenz (EFV) and DRV/r when either of these drugs was taken in combination with two NRTIs,[35,36]. 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. DOR also has a distinct resistance pathway and a potentially higher barrier to resistance than earlier NNRTIs, although not comparable to that of boosted PIs or second-generation INSTIs.[37-40]

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/or CD4 counts <200 cells/mm^3 and is subject to numerous drug–drug interactions.[41] 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

For people in whom ABC, TDF, or TAF cannot be used or are not optimal, the Panel recommends DTG/3TC **(AI).** For the unique situation of individuals needing to avoid TFV and ABC and who are not candidates for DTG/3TC, the Panel recommends DRV/r plus 3TC **(BI)** or FTC **(BII),** or DRV/c plus 3TC **(BII)** or FTC **(BII).** Several other NRTI-sparing 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. Tenofovir-

sparing regimens **should not be used** in individuals with HBV unless entecavir is taken along with the ARV regimen.

Knowledge Gaps

- Research is needed on the efficacy of boosted DRV plus DTG as an initial two-drug regimen.
- Further research is needed to determine whether certain ARV medications or regimens have fewer cardiometabolic complications.
- Research is needed on the safety and efficacy of ARV regimens with extended dosing intervals as initial therapy.

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Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

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This table guides clinicians in choosing an initial antiretroviral (ARV) regimen according to various individual and regimen characteristics and specific clinical scenarios. ARV drugs/regimens that are listed as *Recommended Initial Regimens for Most People With HIV* or *Initial Antiretroviral Regimens for Certain Clinical Scenarios* are included in this table. 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 Advantages and Disadvantages of Antiretroviral Components for additional information regarding the advantages and disadvantages of particular ARV medications recommended to be used as part of initial therapy.

Individual 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	**Do not use** RPV-based regimens.	Higher rates of virologic failure have been observed in those with high pre-treatment HIV RNA levels.
	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** • BIC/TAF/FTC, *or* • DTG plus (TAF or TDF)[a] plus (3TC or FTC) 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 increased risk of treatment failure with DTG resistance.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Individual 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, Use:** • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC) **If No INSTI Resistance Is Identified, Use:** • BIC/TAF/FTC, *or* • DTG plus (TAF or TDF)[a] plus (3TC or FTC), *or* • DTG/3TC	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.
	No prior exposure to CAB-LA for PrEP *and* rapid ART initiation is desired (i.e., before drug resistance results are available)	**Use** • 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.**
	Prior exposure to INSTI-based PEP *or* suspected acquisition from someone with virologic failure on an INSTI-based regimen	• Obtain INSTI genotypic resistance test and start one of the following regimens: o BIC/TAF/FTC, *or* o DTG plus (TAF or TDF)[a] plus (3TC or FTC)	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, and because selection of INSTI-resistant virus is likely to be uncommon in the setting of INSTI-based PEP, 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

Individual or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics	A one-pill, once-daily regimen is desired.	**STR Options as *Recommended Initial Regimens For Most People With HIV*:** • BIC/TAF/FTC • DTG/3TC • DRV/c/TAF/FTC (if history of CAB-LA use as PrEP without INSTI genotype results) **STR Options as *Initial ARV Regimens For Certain Clinical Scenarios*:** • DOR/TDF/3TC • DTG/ABC/3TC • RPV/TAF/FTC	**Do not use** DTG/ABC/3TC if the person is HLA-B*5701 positive. **Do not use** DTG/ABC/3TC or DTG/3TC in the setting of HBV coinfection without another potent, high barrier HBV agent (i.e., entecavir). **Do not use** RPV/TAF/FTC if HIV RNA is >100,000 copies/mL and/or CD4 count is <200 cells/mm^3.
	Food effects	BIC-, DOR-, or DTG-based regimens can be taken without regard to food.	Oral bioavailability of these regimens is not significantly affected by food.
		DRV/r- or DRV/c-based regimens and RPV/TAF/FTC should be taken with food.	Food improves absorption of these regimens.
Presence of Other Conditions	Chronic kidney disease	**Avoid** TDF, if possible, for CrCl <60 mL/min **Avoid** TAF for CrCl <30 mL/min (unless on HD) Refer to Appendix B for specific ARV dosing recommendations in people with renal impairment. For people with progressively declining renal function, consider avoiding all TFV-containing (TAF or TDF) regimens.	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in people using TDF in conjunction with RTV- or COBI- containing regimens. TAF has less impact on renal dysfunction than TDF. If a TDF- or TAF-based regimen cannot be used in the setting of HBV coinfection or unknown HBV status, use entecavir (see HBV/HIV Coinfection).

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Individual or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in people with Child-Pugh class B or C disease.	Refer to Appendix B for specific dosing recommendations. People with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	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.	See Weight Gain in People With Treated HIV for more information.
	Osteoporosis	**Avoid TDF,** if possible.[a]	TDF is associated with decreases in BMD, along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia, especially with RTV- or COBI-boosted regimens. TAF[a] and ABC are associated with smaller declines in BMD than TDF.
	Psychiatric illnesses	**Consider avoiding** RPV-based regimens. People 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. Refer to the Liverpool HIV Drug Interaction Checker for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Individual or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Cardiac QTc interval prolongation	**Consider avoiding** RPV-based regimens if the person is taking other medications with known risk of Torsades de Pointes or in people 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.	Evidence increasingly supports a relationship between ABC and major CV events.
	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.
	History of poor adherence to non-ARV medications or inconsistent engagement in care	Consider using regimens with a high genetic barrier to resistance, such as BIC, DTG, or a boosted PI.	In people with inconsistent adherence, DRMs are less likely to emerge if they are on regimens with 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** without TFV. **If TDF and TAF Are Contraindicated** • Entecavir should be added to a fully suppressive ARV regimen (see HBV/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. However, 3TC and FTC are insufficient for HBV treatment when used alone due to the emergence of resistance.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Individual or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Concomitant use with rifamycin antibiotics (e.g., rifabutin, rifampin, and rifapentine)	Recommended regimens may require dose adjustment. See the drug–drug interaction tables (see the Liverpool HIV Drug Interaction Checker).	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; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450; DOR = doravirine; DRM = drug resistance mutation; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HD = hemodialysis; HLA = human leukocyte antigen; 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 24, 2026
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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 *Recommended Initial Regimens for Most People With HIV* and *Initial Antiretroviral Regimens for Certain Clinical Scenarios* 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 or FTC	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 or FTC** • No notable adverse effects	**ABC** • HSR to ABC is associated with the presence of HLA-B*5701 allele.[a] • Evidence increasingly supports a relationship between ABC and major CV events.

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options for People Without Prior Antiretroviral Treatment

Characteristics	TAF/FTC	TDF/FTC	TDF/3TC	3TC or FTC	ABC/3TC
Other Considerations	• Also used for HBV treatment. Discontinuation may precipitate HBV flare. • See Appendix B for dosing recommendations in people with renal insufficiency. • Some studies reported less weight gain and lower LDL, HDL, TC, and triglycerides with TDF than with TAF. • TDF should be avoided, if possible, in people with renal disease (CrCl <60 mL/min) and/or osteopenia/osteoporosis. • For people with progressively declining renal function, consider avoiding TDF and TAF.			• 3TC or FTC or ABC/3TC **should not be used** as treatment for HBV without adding a potent anti-HBV therapy, such as tenofovir or entecavir. • Consider alternative ARV medications in place of ABC in people with higher underlying ASCVD risk or known ASCVD **(All).**	

[a] 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; ASCVD = atherosclerotic cardiovascular disease; BIC = bictegravir; BMD = bone mineral density; CrCl = creatinine clearance; 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

Ten nucleos(t)ide reverse transcriptase inhibitors (NRTIs) have been approved by the U.S. Food and Drug Administration (FDA). Zidovudine (ZDV) was the first ARV drug approved in 1987. Several older NRTIs are no longer available (didanosine [ddI], stavudine [d4T], and zalcitabine [ddC]) or are rarely used (ZDV) in clinical practice in the United States because of high rates of serious toxicities, including 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 ddC, ddI or d4T use. Therefore, these agents are no longer recommended by the Panel for adults or adolescents. The incidence of these complications is substantially lower with the NRTIs that are currently recommended as initial antiretroviral therapy (ART), which include abacavir (ABC), emtricitabine (FTC), lamivudine (3TC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF).[1,2] A new NRTI, islatravir, was approved by the FDA to use in combination with doravirine (DOR) as a switch regimen for people with viral suppression (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).

TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are part of *Recommended Initial Regimens for Most People With HIV*. In addition, 3TC may be used as a single NRTI with dolutegravir (DTG), except in individuals in whom ART is to be started before the results of HIV genotypic resistance tests are available and when Hepatitis B status is unknown. DTG/3TC **is not recommended** for people with hepatitis B virus (HBV), unless entecavir is added. *Recommended Initial Regimens for Most People With HIV* and *Initial Antiretroviral Regimens for Certain Clinical Scenarios* 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. Both TAF and TDF are recommended options 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 as 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, increasing data continue to support an association between ABC and an increased risk for serious cardiovascular events.[5-8]

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, 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),[9] 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.[10]
- 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.[10] Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through Week 96.[11] 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.[12]

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%).[13] 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 participants in the DRV/c/TAF/FTC arm versus 88% in the DRV/c plus TDF/FTC arm. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.[14]

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 ($P = 0.03$).[15]

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.[16] 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 BMD 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 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.[17] 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.[17]

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 to be noninferior to DTG plus TDF/FTC in ART-naive adults with HIV RNA <500,000 copies/mL and eGFR ≥50 mL/min.[18,19]
- The DOLCE study randomized 230 treatment-naive individuals with CD4 T lymphocyte (CD4) cell count ≤200 cells/mm^3 2:1 to receive DTG/3TC or DTG plus TDF/3TC or TDF/FTC.[20] At baseline, the median CD4 count was 109 cells/mm^3 and viral load 180,000 copies/mL, with 23% having >500,000 copies/mL. The study demonstrated noninferiority between arms and no emergent resistance to integrase strand transfer inhibitors (INSTIs) or NRTIs in either group. Among participants with a pre-treatment viral load >500,000 copies/mL, there was no significant difference in virologic response between the DTG/3TC and triple therapy arms. Although the GEMINI-1 and

GEMINI-2 studies excluded those with a screening viral load >500,000 copies/mL, this study supports the use of the two-drug regimen in this population.

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 (see the Integrase Strand Transfer Inhibitor-Based Regimen section).[21-24]

- 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, the time to first adverse event was also shorter in the ABC/3TC groups.[21]
- 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.[23]
- 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 in the TDF/FTC arm compared with 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%).[22]

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 viral suppression, TAF had more favorable effects on renal biomarkers and BMD than TDF.
- For people with progressively declining renal function, consider avoiding TAF. TAF should be avoided for creatinine clearance (CrCl) <30 mL/min (unless on hemodialysis).

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.[9,12,25]

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[26-28] and ABC.[27] 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.[26] See the Weight Gain in People With Treated HIV section for more information.

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.[29] 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, 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).[17]
- Discontinuation of TAF can precipitate an HBV flare if no other potent, high barrier-to-resistance HBV-active drug (i.e., entecavir) is in the regimen.
- 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] See the Perinatal Guidelines for more information on ARV use during pregnancy.

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 *Initial Antiretroviral Regimens for Certain Clinical Scenarios* when given with RPV **(BII),** DOR **(BIII),** RTV-boosted DRV (DRV/r) **(BI),** or DRV/c **(BI).**

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, raltegravir, and DTG in randomized clinical trials.[30-37]

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.[15]

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.[15]

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). In people who have preexisting renal insufficiency (CrCl <60 mL/min),[46] use of TDF should be avoided, if possible. If TDF is used, a dose adjustment is required if the person's CrCl falls below 50 mL/min (see Appendix B for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In people with HBV/HIV, 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).
- Discontinuation of TDF can precipitate an HBV flare if no other potent, high barrier-to-resistance HBV-active drug (i.e., entecavir) is in the regimen.

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 **(AI),**

- As recommended NRTI combinations for initial ART when combined with DRV/c or DRV/r for people who have a history of long-acting injectable cabotegravir (CAB-LA) use as PrEP, pending the results of genotypic resistance testing **(AIII),**
- As part of *Initial Antiretroviral Regimens for Certain Clinical Scenarios*.

- TDF should be avoided, if possible, in people with renal disease (CrCl <60 mL/min) 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 load and lower CD4 count 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

- FTC and 3TC are generic in the United States and coformulated with other drugs (see Table 8a above).
- Both 3TC and FTC have activity against HBV but are insufficient for HBV treatment when used alone due to the emergence of resistance. People with HBV should also receive another potent HBV drug such as TAF, TDF, or entecavir.
- Discontinuation of FTC or 3TC can precipitate a flare in HBV if no other HBV-active drugs (i.e., TAF, TDF, or entecavir) are in the regimen.
- See Appendix B 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 or Emtricitabine as a Single Nucleoside Reverse Transcriptase Inhibitor

- Based on the GEMINI-1 and GEMINI-2 studies,[19] which found DTG plus 3TC to be noninferior to DTG plus TDF/FTC in ART-naive people with HIV RNA <500,000 copies/mL, and the DOLCE study,[20] which found no significant difference between DTG/3TC and triple therapy in those with HIV RNA >500,000 copies/mL, the single NRTI combination regimen of DTG/3TC can be used regardless of baseline viral load.
- In the ANDES trial, 336 participants were randomized 1:1 to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC.[51] This study was conducted in Argentina using 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/mL, and 23% of participants had HIV RNA >100,000 copies/mL. At Week 48, 91% of participants receiving dual therapy and 93% of those receiving triple therapy achieved an HIV RNA <50 copies/mL, demonstrating noninferiority of the dual therapy regimen.[51] The rates of viral suppression among study participants with baseline HIV RNA >100,000 copies/mL were similar in the dual- and triple-therapy groups (87% and 90%, respectively).

Other Factors and Considerations

- 3TC with DTG is available as an STR.
- 3TC and FTC are active against HBV but are insufficient for HBV treatment when used alone due to the emergence of resistance.
- Discontinuation of 3TC or FTC can precipitate a flare in HBV if no other HBV-active drug (i.e., TAF, TDF, entecavir) is 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, whereas the dose for HBV is 100 mg daily.
- See Appendix B 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*.
- DRV/r + (3TC [**BI**] or FTC [**BII**]) or DRV/c + (3TC or FTC) (**BII**) as *Initial Antiretroviral Regimens for Certain Clinical Scenarios*.

These regimens are **not recommended** for individuals—

- With HBV coinfection, unless receiving entecavir.
- With unknown HBV serostatus.
- Without results from genotypic resistance testing for reverse transcriptase.
- For whom rapid ART initiation is planned.

DTG/3TC is **not recommended** in people who have received CAB-LA as PrEP and do not have INSTI genotype resistance testing results available demonstrating DTG sensitivity.

Abacavir/Lamivudine

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in people who are ART-naive.[24,52-54]

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.[55,56] HLA-B*5701 testing should be performed if ABC use 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.[57-64] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[65-69]
- A recent analysis of the REPRIEVE trial, a double-blind, multicenter, placebo-controlled study of pitavastatin versus placebo, examined the effects of both prior and current ABC use on major adverse cardiovascular events (MACE).[7] Among 7,769 participants, 9.2% had prior exposure to ABC at enrollment (median duration: 3 years), and 12.7% were receiving ABC at study entry (median duration: 1.47 years). In adjusted analyses, both former (adjusted hazard ratio [aHR] 1.62; 95% confidence interval [CI], 1.14–2.30) and current ABC use (aHR 1.41; 95% CI, 1.01–1.96) were associated with an increased hazard of MACE.
- A second REPRIEVE analysis compared ABC- versus TFV-based backbones at trial entry with respect to the risk of first MACE.[8] Among 6,356 people with HIV, 883 were receiving ABC. Baseline-adjusted estimates suggested a higher hazard of first MACE with ABC compared with TDF (hazard ratio [HR] 1.4; 95% CI, 0.9–2.1) and TAF (HR 1.5; 95% CI, 0.9–2.3).
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association; however, the evidence increasingly supports a relationship between ABC and MACE.

Other Factors and Considerations

- ABC/3TC is available as a coformulated tablet and as a coformulated STR with DTG.
- Generic formulations of ABC and 3TC are available separately and as a coformulated tablet.

- 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 *Initial Antiretroviral Regimens for Certain Clinical Scenarios* **(BI)** (see Integrase Strand Transfer Inhibitor–Based Regimens as Initial Antiretroviral Therapy for discussion regarding the clinical efficacy data for DTG/ABC/3TC).
- ABC/3TC used in combination with DRV/r or DRV/c is also recommended as part of *Initial Antiretroviral Regimens for Certain Clinical Scenarios* **(BII).**
- Consider alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known ASCVD **(AII).** See Cardiovascular Complications in People With HIV for more information.

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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Integrase Strand Transfer Inhibitor–Based Regimens as Initial Antiretroviral Therapy

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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 for 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
Adverse Reactions	• ↑ CPK • 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 the Liverpool HIV Drug Interaction Checker for recommendations regarding dosing separations and these drugs.	

Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy–Naive Patients

	BIC	DTG
Other Key Potential Drug Interaction Mechanisms	P-gp substrate, UGT1A1 substrate, OCT2 and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate, OCT2 inhibitor, potential MATE1 inhibitor
Other Factors	Not recommended for initial therapy in those with a history of CAB-LA use as PrEP unless INSTI sensitivity is documented on genotypic resistance testing. 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; CAB-LA = long-acting injectable cabotegravir; 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; PrEP = pre-exposure prophylaxis; 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 initial antiretroviral therapy (ART). 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, including a low barrier to resistance. In addition, because EVG must 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), DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or lamivudine [3TC]), and DTG/3TC are recommended for most people with HIV (see Appendix A, Table 4 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 Recommended Initial Regimens for Most People With HIV and Initial Antiretroviral Regimens for Certain Clinical Scenarios (also see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).

Panel's Recommendations for Integrase Strand Transfer Inhibitor–Based Regimens

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 *Recommended Initial Regimens for Most People With HIV*):

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF) with (FTC or 3TC) **(AI)**

- DTG/3TC **(AI),** except for individuals—
  - With hepatitis B virus (HBV) coinfection, unless on entecavir.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

Several scenarios exist in which an individual or partner may have prior INSTI exposure. For people who previously received 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).** INSTI resistance has been reported in people who acquired HIV following exposure to CAB-LA as PrEP.[1] If treatment is initiated before genotypic test results are available, boosted darunavir (DRV) plus (TAF or TDF) with (FTC or 3TC) should be used, pending INSTI resistance results **(AIII).** See *Recommended Initial Regimens for Most People With HIV* for more details.

For the following groups, an INSTI genotype test should be obtained prior to beginning an INSTI-based regimen, but an INSTI-based regimen can be started before the return of genotype results (see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).

- People who potentially acquired HIV from a partner with virologic failure while on an INSTI, because of the low rates of transmitted INSTI resistance in the United States
- People who have never used CAB-LA for PrEP and who acquired HIV despite using INSTI-based post-exposure prophylaxis, because selection of INSTI-resistant virus is likely to be uncommon in this setting

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 or when DTG/3TC cannot be used. Concerns about renal- or bone-associated adverse events should be weighed against cardiovascular disease risk when considering ABC use, especially in people with higher underlying atherosclerotic cardiovascular disease (ASCVD) risk or known ASCVD. See Cardiovascular Complications in People With HIV for more information. 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 are ART-naive, initiation of INSTI-based regimens has been associated with greater weight increases than with non-nucleoside reverse transcriptase inhibitor (NNRTI)– or boosted protease inhibitor (PI)–based 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 efavirenz (EFV).[8,12-14] Weight gain was also greater in those initiating TAF than in those initiating 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 increases are still unclear. Specific ARV classes or medications, including INSTI- or TAF-based regimens, should not be avoided to prevent or reduce weight gain.

Integrase Strand Transfer Inhibitor Use in Women of Reproductive Potential

Clinicians should refer to the Perinatal Guidelines for detailed recommendations on INSTI-based ARV regimens throughout conception, pregnancy, and postpartum care.

- Earlier data from a birth outcomes surveillance study in Botswana raised concern about an increased risk of neural tube defects (NTDs) of 0.9% in infants born to women who were receiving DTG at the time of conception.[17] 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 that of those on non-DTG regimens at the time of conception.[18] Based on these data, DTG (with [TDF or TAF] plus [3TC or FTC]) is now one of the *Preferred* INSTIs during pregnancy. See the Perinatal Guidelines for further discussion.
- BIC is also recommended as a *Preferred* INSTI during pregnancy based on safety and PK data in pregnancy. See the Perinatal Guidelines for more details.
- DTG/3TC is recommended as an *Alternative* ART regimen during pregnancy. 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, given with or without food.

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/TAF/FTC 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.[19]
  - Week 144 follow-up from both trials demonstrated non-inferiority of the BIC/TAF/FTC regimen to both DTG-containing regimens, with high levels of virologic suppression and no treatment-emergent resistance.[14]
  - The open-label, multicenter LAPTOP trial randomized 447 ART-naive participants with advanced HIV disease to receive either BIC/TAF/FTC or darunavir/cobicistat (DRV/c)/TAF/FTC. Through 48 weeks, the primary composite outcome (the time to first occurrence of specified virologic or clinical event) was observed in 22% of participants in the

BIC/TAF/FTC group and 32% in the DRV/c/TAF/FTC group, demonstrating non-inferiority of BIC/TAF/FTC. At Week 48, HIV RNA <50 copies/mL was achieved by 69% of participants in the BIC/TAF/FTC group and 61% in the DRV/c/TAF/FTC group. Compared with the DRV/c/TAF/FTC group, participants in the BIC/TAF/FTC group were more likely to achieve an HIV RNA <50 copies/mL at Week 4 (16% vs. 1%), Week 8 (35% vs. 7%), and Week 12 (46% vs. 17%).[20]

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: Refer to the Liverpool HIV Drug Interaction Checker for information on 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.
- BIC is an inhibitor of the drug transporters, organic cation transporter 2 (OCT2) and multidrug and toxic compound extrusion 1 (MATE1); 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 0.11 mg/dL by Week 144).[21] 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. A retrospective analysis of data from seven switch trials found 20 individuals with preexisting INSTI-related resistance mutations (based on history or proviral DNA testing) showed maintenance of viral suppression in 19 people after a switch to BIC and viral suppression after beginning BIC in 1 person without prior ARV treatment.[23] However, data are currently insufficient 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)** who **do not** have a history of using CAB-LA as PrEP, unless INSTI sensitivity is documented on genotypic drug resistance testing (see *Recommended Initial Regimens for Most*

People With HIV and Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios 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 non-inferior 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.[12,24,25]

Dolutegravir Plus Two NRTIs Versus Other INSTIs Plus Two NRTIs

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared with 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).[15,19,24,26]

Dolutegravir Plus Two NRTIs Versus Efavirenz 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.[27] At Week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[28]
- The ADVANCE trial, an open-label, non-inferiority 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 non-inferior to the EFV-based 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.[13]

Dolutegravir 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 DRV/r-based regimens.[29] 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.[30]
- The ADVANZ-4 trial, a Phase 4 open-label study, enrolled and randomized 104 ART-naive adults with advanced HIV (CD4 T lymphocyte [CD4] cell counts <100 cells/mm^3) to receive DTG plus ABC/3TC or DRV/r plus ABC/3TC. Virologic response was similar at 48 weeks but occurred

sooner in the DTG arm, with a significantly higher proportion of participants in the DTG arm achieving undetectable viral loads at Weeks 4 and 12.[31]

Dolutegravir/Lamivudine

- 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 non-inferior 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 achieving HIV RNA <50 copies/mL.[32] 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 non-inferiority 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]).[32]
- In the DOLCE study, 230 treatment-naive individuals with CD4 count ≤200 cells/mm^3 were randomized 2:1 to DTG/3TC or DTG plus TDF/3TC or TDF/FTC. At baseline, the median CD4 count was 109 cells/mm^3 and viral load 180,000 copies/mL, with 23% having viral load >500,000 copies/mL. The study demonstrated non-inferiority between the study arms, with no emergent resistance to INSTIs or NRTIs in either group. Among participants with a pre-treatment viral load >500,000 copies/mL, there was no significant difference in virologic response between the DTG/3TC and the triple therapy arm. Although the GEMINI-1 and GEMINI-2 studies excluded those with baseline viral load >500,000 copies/mL, this study supports the use of DTG/3TC in this population.[33]

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.[7-10] 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.[2,3,34,35] 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.[36] Neuropsychiatric events rarely led to DTG discontinuation.

Drug–Drug Interactions

Note: See the Liverpool HIV Drug Interaction Checker for a comprehensive list of potential INSTI-related drug–drug interactions.

- Whereas BIC is a major CYP3A4 substrate, DTG is a minor substrate and is therefore less impacted by CYP3A4-mediated interactions, allowing coadministration with certain medications that cannot be coadministered with BIC; dose adjustment to DTG twice daily may be necessary.
- DTG oral absorption may be reduced when the ARV drug is coadministered with polyvalent cations.

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 (with a mean increase of 0.15 mg/dL after 96 weeks).[37]
- 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* who **do not** have a history of using CAB-LA as PrEP, unless INSTI sensitivity is documented on genotypic drug resistance testing (see *Recommended Initial Regimens for Most People With HIV* and Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios for more detailed recommendations):
  - DTG plus (TAF or TDF) with (FTC or 3TC) **(AI)**
  - DTG/3TC **(AI)—not recommended** for those with HBV coinfection unless on another HBV-active drug (i.e., entecavir), those with unknown HBV serostatus, or those in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase are available. DTG/3TC is not appropriate for rapid ART initiation.
- 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 have concerns about renal or bone toxicities associated with TAF or TDF or who cannot use DTG/3TC. Concerns about renal- or bone-associated adverse events should be weighed against cardiovascular disease risk when considering ABC use, especially in individuals with higher underlying ASCVD risk or known ASCVD. See Cardiovascular Complications in People With HIV for more information. This regimen should not be used in people with HBV 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

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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 ARV Regimens for Certain Clinical Scenarios*	DOR/TDF/3TC	RPV/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	• Skin rash • SJS/TEN (rarely observed) • DRESS (rarely observed)	• Depression • Headache • Skin rash • SJS/TEN (rarely observed) • DRESS (rarely observed) • 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 contraindicated;** see the Liverpool HIV Drug Interaction Checker for dosing recommendations when RPV is coadministered with an H2 blocker or antacids.

[a] See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression and Appendix A, Table 6 for information regarding injectable RPV.

Key: 3TC = lamivudine; ARV = antiretroviral; CYP = cytochrome P450; DOR = doravirine; DRESS = drug reaction with eosinophilia and systemic symptoms; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis

Summary

Non-nucleoside reverse transcriptase (NNRTI)–based regimens have demonstrated virologic potency and durability. Earlier NNRTIs (efavirenz [EFV] and nevirapine [NVP]) have some major disadvantages, including the prevalence of pre-treatment NNRTI resistance,[1] a low barrier for the development of resistance, the potential for drug–drug interactions, and a high rate of toxicities. The Panel on Antiretroviral Guidelines for Adults and Adolescents (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 recommended in adults and adolescents due to a relatively high potential for adverse effects, including serious hepatotoxicity and skin reactions, including Stevens-Johnson syndrome. This section of the guidelines focuses on rilpivirine (RPV) and doravirine (DOR), which are the two NNRTIs currently recommended as part of *Initial Antiretroviral Regimens for Certain Clinical Scenarios* (also see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios). There is no clinical trial comparing the efficacy of these two NNRTIs as initial antiretroviral regimens.

Resistance testing should be performed before initiation of an NNRTI-based regimen in people without prior antiretroviral therapy (ART) experience. Thus, these regimens are not appropriate for rapid ART initiation when ART is to be started before the results of HIV genotypic resistance testing are available.

Doravirine

DOR is approved for use in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as initial ART for people with HIV. DOR has a distinct resistance pathway and a potentially higher barrier to resistance than earlier NNRTIs, though not comparable to that of boosted protease inhibitors or second-generation integrase strand transfer inhibitors.[2] Data suggest that DOR can retain activity in the setting of common, single NNRTI resistance–associated mutations (K103N, V106I, Y181C, G190A).[3-6]

Efficacy in Clinical Trials

Doravirine Plus Two NRTIs Versus Efavirenz Plus Two NRTIs

In the DRIVE-AHEAD trial, 734 treatment-naive participants received either DOR/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or EFV/TDF/emtricitabine (FTC), both as a daily fixed-dose combination tablet.[7] At 96 weeks, DOR/TDF/3TC was non-inferior to EFV/TDF/FTC, with 77.5% and 73.6% of participants achieving HIV RNA <50 copies/mL, respectively. Neuropsychiatric side effects and rash were more common in the EFV arm. Virologic rebound and virologic nonresponse were similar in the DOR/TDF/3TC (9.3%) and EFV/TDF/FTC (7.7%) treatment groups. Among participants in the DOR arm who had protocol-defined virologic failure with genotypic resistance testing available at the time of failure, 7 of 21 (33.3%) had NNRTI resistance, and 6 of 21 (28.6%) had NRTI resistance. In the EFV arm, 10 of 15 (66.7%) participants had NNRTI resistance and 5 of 15 (33.3%) had NRTI resistance.

Doravirine Plus Two NRTIs Versus Darunavir/Ritonavir Plus Two NRTIs

In the DRIVE-FORWARD trial, 769 treatment-naive participants received DOR or darunavir/ritonavir (DRV/r) once daily along with two investigator-selected NRTIs, either abacavir (ABC)/3TC or TDF/FTC.[8] At 96 weeks, DOR was non-inferior to DRV/r, with 73% versus 66% of study participants achieving HIV RNA <50 copies/mL, respectively. Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.

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. Protocol-defined virologic failure was similar in the DOR and DRV/r groups (9% vs. 11%). Treatment-emergent resistance was observed in two participants in the DOR group (resistance to both DOR and to FTC/3TC) and one participant in the DRV/r group (FTC/3TC resistance).

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. At 192 weeks, 83% of participants who continued on DOR and 81% of participants who switched to DOR maintained viral suppression.[9] Additional virologic failures in the open-label extension were uncommon, occurring in 2.7% of participants who continued DOR and 5.2% of those who switched to DOR after Week 96. Treatment-emergent phenotypic resistance to DOR following Week 96 was observed in four participants: three in the delayed switch arm and one in the initial therapy arm.[10]

Other Factors and Considerations

- DOR is available as a single-drug 100-mg tablet[11] and as part of a three-drug single-tablet regimen (STR) that contains DOR 100 mg/TDF 300 mg/3TC 300 mg.[12] All formulations are dosed once daily, with or without food.
- DOR has not been studied with tenofovir alafenamide (TAF)/FTC in clinical trials as initial ART. However, based on the similar efficacy of TAF and TDF in other clinical trials, DOR plus TAF/FTC is expected to have virologic efficacy comparable to DOR/TDF/3TC.
- DOR is also available as a two-drug STR containing DOR 100 mg/islatravir (ISL) 0.25 mg, which is approved as a switch regimen in people with viral suppression.[13] Because DOR/ISL has not been approved by the U.S. Food and Drug Administration (FDA) for initial therapy, the Panel cannot recommend it for use in those who are not virally suppressed on ART.
- DOR is primarily metabolized by the cytochrome P450 (CYP) 3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see the Liverpool HIV Drug Interaction Checker). DOR is not a CYP3A4 inducer or inhibitor; thus, it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Please refer to the Perinatal Guidelines for recommendations on the use of DOR in pregnancy.
- Because clinical trial data for the combination of DOR plus ABC/3TC is limited, 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 *Initial Antiretroviral Regimens for Certain Clinical Scenarios*.
- DOR-based regimens are not appropriate for rapid ART initiation when ART is to be started before the results of HIV genotypic resistance testing are available.

Rilpivirine

Oral RPV is approved for use in combination with two NRTIs as initial ART for people with HIV who have pre-treatment viral load ≤100,000 copies/mL.[14] In people treated with RPV, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs.

RPV is also approved as part of a long-acting injectable regimen combined with cabotegravir (LA CAB/RPV) and as an oral STR combined with dolutegravir (DTG) for use in people with viral suppression (HIV RNA <50 copies/mL). These two regimens have not been studied in treatment-naive populations and **are not recommended** as initial ART. See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for discussion of LA CAB/RPV and DTG/RPV.

Efficacy in Clinical Trials

Rilpivirine Plus Two NRTIs Versus Efavirenz Plus Two NRTIs

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs as initial ART.[15] At 96 weeks, RPV was non-inferior to EFV overall. However, among the RPV-treated participants, the rate of virologic failure was higher in those with pre-treatment CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3 and in those with pre-treatment viral loads >100,000 copies/mL. NNRTI and NRTI resistance were more frequently found in RPV-treated participants with virologic failure.
- 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[16] were similar to those reported at 48 weeks.[17] RPV was non-inferior to EFV overall. RPV was superior to EFV in participants with pre-ART viral loads ≤100,000 copies/mL and non-inferior 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 participants 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/cobicistat/TAF 10 mg/FTC.[18]

Adverse Effects

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of central nervous system 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 whether the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations

- For initial ART, oral RPV is formulated as a single-drug tablet and as an STR in combination with TAF/FTC or TDF/FTC. Among available STRs, RPV/TDF/FTC is no longer recommended by the Panel for initial therapy.
- The STR of RPV/TAF/FTC is given once daily and must be administered with a meal.

- 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 the Liverpool HIV Drug Interaction Checker for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A4 enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see the Liverpool HIV Drug Interaction Checker).
- At doses above the approved dose of 25 mg, RPV may cause QTc (QT corrected for heart rate) 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 *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 *Initial Antiretroviral Regimens for Certain Clinical Scenarios*, largely to retain an STR option containing an NNRTI and TAF.
- Use of RPV/TAF/FTC **(BII)** should be limited to people with pre-treatment viral load ≤100,000 copies/mL and CD4 count ≥200 cells/mm^3.
- RPV/TAF/FTC is not appropriate for rapid ART initiation when ART is to be started before the results of HIV genotypic resistance testing are available.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

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Protease Inhibitor–Based Regimens

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Table 8d. Characteristics of Protease Inhibitor Options as Initial Antiretroviral Therapy

Characteristic	DRV
Dosing Frequency	Once daily
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	CYP3A4 substrate, inhibitor
Other Significant Drug Interactions	N/A

Key: COBI = cobicistat; CYP = cytochrome P450; DRV = darunavir; DRV/c = darunavir/cobicistat; FTC = emtricitabine; N/A = not applicable; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

Ten protease inhibitors (PIs) have been approved by the U.S. Food and Drug Administration. Currently used PI-based regimens use pharmacokinetic (PK) enhancement (also called PK boosting) with either cobicistat (COBI) or ritonavir (RTV) to increase concentrations and prolong the half-lives of the PI. These regimens have demonstrated virologic potency, durability in people who are antiretroviral therapy (ART)–naive, and a high barrier to resistance. Because the older PIs, such as lopinavir and atazanavir (ATV), have disadvantages—such as greater pill burden, lower efficacy, or increased toxicity—they are no longer recommended. Boosted darunavir (DRV), when combined with one or two nucleoside reverse transcriptase inhibitors (NRTIs), is the only PI recommended for initial therapy (see *Recommended Initial Regimens for Most People With HIV* and *Initial Antiretroviral Regimens for Certain Clinical Scenarios*.

Because transmitted PI resistance is uncommon, a boosted DRV–based regimen (with two NRTIs) is 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, similar to a second-generation INSTI, a boosted DRV–based regimen can be used for rapid ART initiation and is the preferred option while awaiting resistance test results for people with a history of long-acting cabotegravir (CAB-LA) use for pre-exposure prophylaxis (PrEP). Similar to what is seen with second-generation INSTIs, few or no resistance mutations are detected when a patient's first regimen fails, which is not the case with NNRTI-based regimens and regimens with a first-

generation INSTI (e.g., raltegravir [RAL] or elvitegravir).[1] Because of their high barrier to resistance, PI-based regimens may be useful for people at risk for poor adherence.

DRV requires PK boosting with either RTV (DRV/r) or COBI (DRV/c) to inhibit the cytochrome P450 (CYP) 3A4 isoenzyme, which may lead to significant drug–drug interactions (see the Liverpool HIV Drug Interaction Checker). The specific characteristics of DRV are listed in Appendix A, Table 5.

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/tenofovir alafenamide (TAF)/emtricitabine (FTC) with DRV/c plus tenofovir disoproxil fumarate (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.[2] 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.[3]
- In the open-label, multicenter LAPTOP trial, 447 adults with advanced HIV disease were randomized to receive either bictegravir (BIC)/TAF/FTC or DRV/c/TAF/FTC. The primary composite outcome was the time to first occurrence of specified virological or clinical event. At 48 weeks, the primary composite outcome was observed in 22% of participants in the BIC/TAF/FTC group versus 32% in the DRV/c/TAF/FTC group, demonstrating noninferiority of BIC/TAF/FTC. At Week 48, 69% and 61% of participants achieved HIV RNA <50 copies/mL in the BIC/TAF/FTC and DRV/c/TAF/FTC groups, respectively. Compared with the DRV/c/TAF/FTC group, participants in the BIC/TAF/FTC group were more likely to achieve HIV RNA <50 copies/mL at Week 4 (16% vs. 1%), Week 8 (35% vs. 7%), and Week 12 (46% vs. 17%).[4]
- The DIAMOND study was a single-arm trial that 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 RNA <50 copies/mL. 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.[5]

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; therefore, DRV/c **is not recommended** as part of initial therapy in pregnancy.[6] 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

- For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting an INSTI-based regimen. If ART is to be started before genotypic testing results are available, DRV/c with (TAF or TDF) plus (FTC or lamivudine [3TC]) can be started **(AIII).**
- The Panel recommends DRV/c plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/c plus abacavir (ABC)/3TC **(BII)** as part of *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 the unique situation in which tenofovir (TFV) and ABC must be avoided and DTG/3TC is not an option, the Panel recommends DRV/c plus (3TC or FTC) **(BII)** (see *Initial Antiretroviral Regimens for Certain Clinical Scenarios*), except for individuals—
  - With hepatitis B virus (HBV) coinfection, unless receiving entecavir.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

Darunavir/Ritonavir

Efficacy in Clinical Trials

With Two Nucleoside Reverse Transcriptase Inhibitors

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 (DRV 800 mg/RTV 100 mg) 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 TDF/FTC or ABC/3TC—in 488 participants who were ART-naive. The rate of viral suppression at Week 96 was significantly higher among those who received DTG than among 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.[7]
- The AIDS Clinical Trial Group (ACTG) study A5257 (ARDENT), a randomized, open-label trial, compared atazanavir/ritonavir (ATV/r) to DRV/r or RAL over 96 weeks, each given with TDF/FTC. A total of 1,809 treatment-naive adults were enrolled. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment due to adverse events.[8]
- 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.[9] At Week 96, DOR was superior to DRV/r in terms of viral suppression (73% vs. 66%).[9] 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).

DRV/r-based regimens have also been assessed in randomized trials as first-line ARV treatment for individuals presenting with advanced HIV, as summarized below.

- In the open label ADVANZ-4 trial, 104 ART-naive adults with advanced HIV (CD4 T lymphocyte cell counts <100 cells/mm^3) were randomized to receive either DTG plus ABC/3TC or DRV/r plus ABC/3TC. Virologic responses were similar at 48 weeks but faster for the DTG arm, with a significantly higher proportion of participants in the DTG arm achieving undetectable viral load at Weeks 4 and 12.[10]

With One Nucleoside Reverse Transcriptase Inhibitor

- In the ANDES trial, 336 ART-naive participants were randomized to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC.[11] This study was conducted in Argentina using a fixed-dose combination of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies/mL, and 23% of participants had HIV RNA >100,000 copies/mL. At Week 48, 91% of participants in the dual-therapy group and 93% of those in the triple-therapy group achieved HIV RNA <50 copies/mL, demonstrating noninferiority with dual therapy.[11] The rates of viral suppression among study participants with baseline HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (87% and 90%, respectively).

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.[8] 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).[12]
- 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.[9]

Other Factors and Considerations

- DRV/r is administered once daily with food.
- 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 the Liverpool HIV Drug Interaction Checker).

- Unlike DRV/c, dose-adjusted DRV/r may be used in pregnancy (see the Perinatal Guidelines for more information).

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 (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).**
- DRV/r plus (TAF or TDF) plus (FTC or 3TC) **(BI)** and DRV/r plus ABC/3TC **(BII)** are also part of *Initial Antiretroviral Regimens for Certain Clinical Scenarios* (also see Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios).
- For the unique situation in which TFV and ABC must be avoided and DTG/3TC is not an option, the Panel recommends DRV/r plus (3TC **[BI]** or FTC **[BII]**) (see *Initial Antiretroviral Regimens for Certain Clinical Scenarios*), except for individuals—
  - With HBV coinfection, unless receiving entecavir.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

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

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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 most people with HIV (see *Recommended Initial Regimens for Most People With HIV* 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 DTG/3TC is the only two-drug regimen currently recommended (as an *Alternative* option) during pregnancy (see the Perinatal Guidelines for more information).

In addition, tenofovir-sparing regimens **are not recommended** in people with chronic hepatitis B virus (HBV)/HIV unless another potent, high-barrier HBV-active drug (i.e., entecavir) is added. Clinicians should refer to HBV/HIV Coinfection for guidance on the 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 T lymphocyte (CD4) cell 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 non-inferiority to DTG plus TDF/FTC with 82% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with a 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]
- In the DOLCE study, 230 treatment-naive participants with CD4 counts ≤200 cells/mm³ were randomized 2:1 to DTG/3TC or DTG plus TDF/(3TC or FTC).[2] At baseline, the median CD4 count was 109 cells/mm^3 and median viral load 180,000 copies/mL, with 23% having

≥500,000 copies/mL. DTG/3TC demonstrated non-inferiority to the three-drug arm, with no emergent resistance to INSTIs or NRTIs in either group. Although the GEMINI-1 and GEMINI-2 studies excluded those with a screening viral load >500,000 copies/mL, this study supports the use of the two-drug regimen in this population.

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),** except for individuals—

- With HBV coinfection, unless a potent high-barrier HBV-active drug (i.e., entecavir) is added (see HBV/HIV Coinfection).
- With unknown HBV serostatus.
- Without results for genotypic resistance testing for reverse transcriptase.
- Who have a history of long-acting cabotegravir (CAB-LA) use as pre-exposure prophylaxis without documented INSTI sensitivity on genotypic resistance testing.
- For whom rapid ART initiation is planned.

Boosted Darunavir Plus Lamivudine or Emtricitabine

- 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.[3] This study was conducted in Argentina and used a fixed-dose combination of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies/mL, 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.[3] 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's Recommendation

For the unique situation in which tenofovir and ABC must be avoided and DTG/3TC is not an option, the Panel recommends DRV/r plus 3TC **(BI)** or FTC **(BII)**, or darunavir/cobicistat plus 3TC **(BII)** or FTC **(BII)** (see *Initial Antiretroviral Regimens for Certain Clinical Scenarios*), **except** for individuals—

- With HBV coinfection, unless a potent high-barrier HBV-active drug (i.e., entecavir) is added (see HBV/HIV Coinfection).
- With unknown HBV serostatus.
- Without results from genotypic resistance testing for reverse transcriptase.
- For whom rapid ART initiation is planned.

Regimens With Some Supporting Data but Not Recommended as Initial Therapy

The Panel **does not recommend** the following NRTI-sparing regimens for initial therapy because of insufficient clinical trial data.

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. However, more virologic failures occurred in the RAL plus DRV/r arm among those with baseline CD4 counts <200 cells/mm^3. A trend toward more failure was also observed among those with pre-treatment HIV RNA ≥100,000 copies/mL.[4] 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.[5,6] 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 with this regimen than with 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 darunavir or rilpivirine (RPV) received DRV/r plus RPV for 48 weeks. Half the participants (18 of 36) had baseline HIV viral loads >100,000 copies/mL. Viral suppression (HIV RNA <50 copies/mL) was achieved in 97% of participants (35 of 36) by Week 36, increasing to 100% by Week 48.[7] 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 2b trial LATTE-2,[8,9] ART-naive participants were first treated with 20 weeks of DTG/ABC/3TC or oral cabotegravir plus 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** 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 Recommended for Most People With HIV or for Certain Clinical Scenarios

Updated: September 24, 2026
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Note: All drugs within an ARV class are listed in alphabetical order. Information based on *Recommended Initial Regimens for Most People With HIV* and *Initial Antiretroviral Regimens for Certain Clinical Scenarios*. See Adverse Effects of Antiretroviral Medications for additional details.

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. • Evidence increasingly supports a relationship between ABC and major CV events.
	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 CrCl ≥30 mL/min • Can be used in people on chronic hemodialysis without dose adjustment	• See text in the NRTI and Weight Gain sections regarding weight changes with TAF when compared with TDF.
	TDF/3TC	• Active against HBV; a recommended dual-NRTI option for people with HBV/HIV coinfection • Coformulated with DOR • Generic formulations are available for TDF, 3TC, or TDF/3TC.	• **Not recommended** for people with CrCl <60 mL/min. The coformulated products **are not recommended** for CrCl <50 mL/min or hemodialysis. • Renal toxicity is associated with TDF use, 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 is associated with TDF use, especially when combined with pharmacologic boosters.

Table 9. Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy Recommended for Most People With HIV or for Certain Clinical Scenarios

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
	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.	• **Not recommended** in people with CrCl <60 mL/min, but if used, requires dose adjustment for CrCl <50 mL/min. The coformulated tablet **is not recommended** if CrCl <30 mL/min or on hemodialysis. • Renal toxicity is associated with TDF use, 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 is associated with TDF use, especially when combined with pharmacologic boosters.
Single NRTI	**3TC or FTC**	• 3TC is coformulated with DTG as STR • Avoids potential toxicities associated with TDF, TAF, or ABC use (as coformulation)	• DTG/3TC, DTG + FTC, and boosted DRV + (3TC or FTC) **are not recommended** for individuals— o With HBV coinfection, unless on another HBV active drug (i.e., entecavir) o With unknown HBV serostatus o Without genotypic resistance testing results o In whom rapid ART initiation is planned
INSTI	**BIC**	• Coformulated with TAF/FTC • 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 the Liverpool HIV Drug Interaction Checker. • CYP3A4 and UGT1A1 substrate; monitor for drug–drug interactions. See the Liverpool HIV Drug Interaction Checker. • Depression and suicidal ideation have been rarely observed (usually in people with preexisting psychiatric conditions). • See text in the INSTI and Weight Gain sections regarding weight gain and INSTI use.

Table 9. Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy Recommended for Most People With HIV or for Certain Clinical Scenarios

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
	DTG	• Coformulated with ABC/3TC and 3TC as STR • No food requirement • Less impacted by CYP3A4-mediated interactions than BIC • 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 the Liverpool HIV Drug Interaction Checker. • CYP3A4 (minor) and UGT1A1 substrate; monitor for drug interactions. See the Liverpool HIV Drug Interaction Checker. • Depression and suicidal ideation have been rarely observed (usually in people with preexisting psychiatric conditions). • See text in the INSTI and Weight Gain sections regarding weight gain and INSTI use.
NNRTI	**DOR**	• Coformulated with TDF/3TC • Fewer CNS side effects compared to EFV and RPV • No food requirement • Potentially higher barrier to resistance than other NNRTIs (but not comparable to that of boosted PIs or second-generation INSTIs)	• Monitor for CYP drug interactions. See the Liverpool HIV Drug Interaction Checker.
	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 risk for virologic failure. • Depression and suicidality • QTc interval prolongation; consider using an alternative to RPV in people with higher risk of Torsades de Pointes, whether due to concomitant medications, prolonged QTc, or other risk factors. • Rash • Transmitted drug 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

Table 9. Advantages and Disadvantages of Antiretroviral Components of Initial Antiretroviral Therapy Recommended for Most People With HIV or for Certain Clinical Scenarios

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
			• Monitor for CYP drug interactions (see the Liverpool HIV Drug Interaction Checker). • Meal requirement • Requires acid for adequate absorption o **Contraindicated** with PPIs. o Use with H2 antagonists or antacids with caution.
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.	• CYP3A4 inhibitors and substrates; monitor for drug interactions. See the Liverpool HIV Drug Interaction Checker. • Skin rash • Food requirement with dosing • GI adverse effects • Increased CVD 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	• Coadministration with TDF **is not recommended** in people with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • DRV/c-based regimens **are not recommended** as initial therapy in pregnancy because levels of COBI and DRV are lower in the second and third trimesters. If women who are pregnant with suppressed viral load on DRV/c-based regimens 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; CrCl = creatinine clearance; CV = cardiovascular; CVD = cardiovascular disease risk; CYP = cytochrome P450; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; 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; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase

References

1. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV.* 2018;5(6):e291-e300. Available at: https://pubmed.ncbi.nlm.nih.gov/29731407.

MANAGEMENT OF PEOPLE WITH HIV AND ANTIRETROVIRAL THERAPY EXPERIENCE

Virologic Failure

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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 the Liverpool HIV Drug Interaction Checker 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 35 (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 A, Table 7 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 the Liverpool HIV Drug Interaction Checker 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

Table 10. Antiretroviral Options for People with HIV and Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a]	Goal
		If failure on EVG or RAL, often have INSTI resistance, but potentially susceptible to DTG Can have 3TC or FTC resistance.	Boosted PI plus two NRTIs (preferably at least one fully active[c]) **(AIII);** *or* 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).**	Resuppression
	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.	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).**	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
		Consult an expert in drug resistance if needed.	Consider enrollment into clinical trials or expanded access programs for investigational agents if available. Discontinuation of all ARV drugs **is not recommended (AI).**	
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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Suboptimal CD4 Cell Recovery Despite Viral Suppression

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Key Considerations and Recommendations
• Suboptimal CD4 T lymphocyte (CD4) cell recovery is associated with increased AIDS- and non–AIDS-related morbidity and mortality among individuals with antiretroviral therapy (ART)–mediated viral suppression. • Promptly initiating ART in people diagnosed early with HIV provides the best opportunity for maximal CD4 cell recovery. • Adding antiretroviral (ARV) drugs to a suppressive ART regimen (ART intensification) does not improve CD4 cell recovery and therefore **is not recommended** for this purpose **(AI).** • Switching ARV drugs or drug classes in people with suppressed viral load does not improve CD4 cell recovery substantially and **is not recommended** for this purpose **(AII).** • Interleukin-2 **is not recommended** to increase CD4 counts because clinical trial data demonstrated no clinical benefit **(AI).** • Other interventions to increase CD4 counts **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 preventive care (e.g., opportunistic infection prophylaxis, vaccinations, cancer screening, statin therapy to reduce cardiovascular risk), addressing modifiable risk factors for chronic disease (e.g., tobacco use, alcohol and substance use, unhealthy diet, sedentary lifestyle), and optimizing management of comorbidities (e.g., hypertension, diabetes).
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

Most people with HIV who achieve and maintain antiretroviral therapy (ART)–mediated viral suppression experience increases in peripheral blood CD4 T lymphocyte (CD4) cell counts over time[1-4] and recovery of CD4 counts to within the normal range (>500 cells/mm^3) of people without HIV.[5-7] However, some people who started ART at low CD4 counts do not experience recovery to the desired immunologic goal of >500 cells/mm^3 despite sustained virologic suppression on ART.[2,3,8] Promptly initiating ART in people diagnosed early with HIV provides the best opportunity for maximal CD4 cell recovery.[9,10]

There is no clear consensus on terminology to use or thresholds that define "suboptimal CD4 cell recovery."[11,12] A common threshold used for "suboptimal CD4 cell recovery" is CD4 ≤500 cells/mm^3 after several years of suppressive ART. The term "immunologic nonresponse" also has been used to describe a lack of CD4 cell recovery, with common thresholds of <200 cells/mm^3 or <350 cells/mm^3 after several years of suppressive ART.[12] Some experts consider an increase of <200 cells/mm^3 above baseline after 24 months as an inadequate immunologic response for people with CD4 counts ≤500 cells/mm^3. The relationship between improved clinical outcomes and higher CD4 counts likely spans all ranges of CD4 counts, although incremental benefits are harder to discern once

CD4 counts reach moderate-to-high levels,[13] especially beyond 500 cells/mm^3. Rarely, people with HIV may experience substantial declines in CD4 counts while maintaining virologic suppression on ART.[14]

Clinical Consequences

Persistently low CD4 counts despite ART-mediated viral suppression are associated with increased risk of morbidity, hospitalizations, and mortality. Data from two large international cohorts of people with HIV initiating ART as early as 1996 showed that individuals with HIV and 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 counts.[15] A multicenter cohort study from Spain of individuals who started ART with low CD4 counts between 2005 and 2019 found that those whose CD4 counts remained <200 cells/mm^3 after 2 years of ART had a 4.6-fold greater risk of mortality than those with CD4 >500 cells/mm^3.[16]

People with CD4 counts <200 cells/mm^3 despite at least 1 year of suppressive ART are at increased risk of AIDS-related and non–AIDS-related events.[17-23] This population is at risk of severe infections (e.g., pneumonia) and is less likely to mount a robust immune response following vaccination.[24] In addition, these individuals have an increased risk of infection-related cancers (e.g., Epstein-Barr virus-associated lymphoma, human papillomavirus–associated malignancies, hepatocellular carcinoma associated with hepatitis B virus [HBV] or hepatitis C virus [HCV]). A cohort study of people with HIV from 1996 to 2020 demonstrated that people with CD4 <200 cells/mm^3 had a 3.5-fold higher risk of infection-related cancers compared to people with CD4 ≥500 cells/mm^3.[25] Another study found that CD4 count <350 cells/mm^3 was associated with non–AIDS-defining, smoking-related, and other malignancies.[26] People with HIV who receive chemotherapy or radiation therapy can also experience CD4 count decline. One study reported a 27% increase in mortality for every 100 cells/mm^3 decrease in CD4 count.[27] Lastly, cardiovascular disease and other comorbidities have also been observed at increased rates in people with low CD4 recovery.[15,28-35]

Pathogenesis

Suboptimal CD4 recovery after ART-mediated virologic suppression is typically associated with higher levels of inflammation and immune activation[36] and is most frequently observed in people with older age, prior AIDS-defining illness, lower nadir CD4 count,[16,37] and some coinfections (e.g., HCV).[38-40] The association of higher inflammation levels with persistently low CD4 counts is likely multifactorial and, to some extent, may be driven by inadequate immunologic control of other chronic viral infections, based on observed decreases in inflammation after treatment of cytomegalovirus and chronic HCV infection.[41,42] Numerous factors have deleterious effects on T-cell survival and proliferation, such as chronic coinfections, a persistently activated innate immune system (due to stimuli such as microbial translocation and dysbiosis), more severe fibrosis of lymph node tissue with disruption of naive T-cell homeostasis, potential senescence of hematopoietic progenitors, and possibly autoantibodies.[43-46]

CD4 count may occasionally decline despite suppressive ART, which may be due to a new medication, a new underlying malignancy, infection, or autoimmune disorder, including the presence of anti-CD4 autoantibodies,[44,45] and/or dysregulation of interleukin-7 (IL-7)–mediated naive T-cell homeostasis or more accentuated immune senescence.[14,47,48]

Alternative Causes of Suboptimal CD4 Cell Recovery

Evaluation of people with suboptimal CD4 cell recovery should begin with identifying modifiable causes, such as concomitant medications that reduce total white blood cells, particularly lymphocytes and CD4 cells. When possible, these drugs should be discontinued and replaced with

alternatives if necessary. Untreated coinfections (e.g., HCV, *Mycobacterium avium* complex, histoplasmosis) and serious medical conditions (e.g., malignancy, autoimmune disease) may also contribute to CD4 lymphopenia, particularly in people with declining CD4 counts (and percentages) while on suppressive ART and in those with CD4 consistently <100 cells/mm^3. Treating coinfections and optimizing management of contributing conditions should be pursued when feasible.

Interventions Tested to Improve CD4 Cell Recovery

For people with suboptimal CD4 cell recovery despite suppressive ART, effective interventions to increase CD4 counts and improve clinical outcomes have not been identified.[49] Strategies to raise CD4 counts by modifying or intensifying ART regimens have been evaluated in clinical trials. Intensification strategy by adding ARV drugs to a suppressive ART regimen does not improve CD4 cell recovery[50-56] and does not reduce morbidity or mortality. Therefore, ART intensification **is not recommended** as a strategy to improve CD4 cell recovery **(AI).** Similarly, switching ARV drugs or classes has not been shown to improve CD4 cell recovery substantially for individuals with viral suppression and **is not recommended (AII).**[57,58]

Therapies targeting immunomodulatory pathways (e.g., interleukin-2 [IL-2], IL-7, growth hormone, thymosin alpha-1) have also been investigated as a strategy to increase CD4 counts.[59] Two large randomized trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of IL-2 for improving CD4 cell recovery. Although there is strong evidence linking low CD4 cell counts with increased morbidity, IL-2 adjunctive therapy did not decrease the risk of clinical events despite substantial increases in CD4 count.[60] Therefore, IL-2 is **not recommended** as a strategy to improve CD4 recovery **(AI).** Dysregulation in IL-7–mediated naive T-cell homeostasis has been reported among people with suboptimal CD4 recovery.[14,47,48] While several early-phase trials of human recombinant IL-7 treatment have shown an increase in CD4 counts among people with HIV on ART, no clinical trials designed to evaluate whether IL-7 treatment confers benefit on clinical outcomes have been performed.[61]

Additional interventions have been studied in early-phase trials, and some have demonstrated improvements in CD4 counts among people with HIV on ART with suboptimal CD4 cell recovery. These studies were not designed to evaluate clinical endpoints. Examples include the use of novel antivirals,[62] repurposed medications,[63,64] probiotics,[65,66] plants and herbal treatments with medicinal properties,[67-69] and other nutritional supplements,[70] as well as human umbilical cord mesenchymal stem cell infusions[71,72] or allogenic natural killer cell immunotherapy.[73] As demonstrated by the IL-2 clinical trial results, randomized trials with clinical endpoints will be needed to establish clinical benefit. Because of the lack of clinical efficacy data from these alternative interventions, the use of adjunct therapies to improve immune recovery **is not recommended,** except in the context of a clinical trial **(AII).**

Prevention of Clinical Consequences

With continuous ART and viral suppression, life expectancy for people with HIV is approaching that of people without HIV. However, persistently low CD4 counts despite ART-mediated viral suppression are associated with higher rates of both AIDS and non–AIDS-related morbidity and mortality over the long term. Reducing AIDS- and non–AIDS-related morbidity and mortality remains a cornerstone of HIV treatment and is especially important for people with suboptimal CD4 recovery, given the increased risk of such outcomes. Risk for opportunistic infections (OIs) is generally low for people on ART with viral suppression, but some primary or secondary prophylaxis may need to be extended for certain OIs among people who do not experience CD4 recovery above certain thresholds (see the Adult OI Guidelines for specific guidance).

Given the increased risk for severe manifestations and/or poor outcomes from infections such as tuberculosis, HBV, and HCV, guidelines for screening for such infections should be followed closely, and treatments should be initiated promptly when indicated. Clinicians should also be vigilant about ensuring that people with HIV are up to date on vaccinations for preventable infections. It should be noted that live virus vaccines are contraindicated for people with CD4 counts <200 cells/mm^3 (see Immunizations for Preventable Diseases in Adults and Adolescents With HIV in the Adult OI Guidelines for detailed recommendations).

For non-AIDS-related morbidities, providers should offer preventive counseling, evaluate and manage cardiovascular risk factors (see Cardiovascular Complications), ensure that screening for malignancies (e.g., colorectal cancer, anal or cervical cancer, hepatocellular carcinoma, lung cancer, breast cancer) is up to date (see Primary Care Guidance), initiate statin therapy when indicated (see Statin Therapy in People With HIV), and provide prompt care and referrals when appropriate.[74] As for all people with HIV, regardless of CD4 count, preventive counseling should address lifestyle modifiable risk factors, including but not limited to smoking cessation, abstinence from alcohol and substance use, dietary modification, regular exercise, and treatment optimization for comorbidities such as hypertension and diabetes.

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Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

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Key Considerations and Recommendations
• Many people with HIV and ongoing HIV viral suppression can be successfully transitioned to alternative regimens and maintain viral suppression. • 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, drug–disease interactions, pill burden, pregnancy, cost, stigma or 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 switch to any regimen that has been shown to be highly effective in people who are ARV-naive **(AI)** or to regimens extensively researched in optimization studies. • For regimen optimization in the setting of existing NRTI resistance, there are two main options: o In many situations, a regimen containing two NRTIs (TAF or TDF plus FTC or 3TC) can be used along with a fully active drug with a high resistance barrier, such as DTG**,** BIC**,** or boosted DRV**.**   o An NRTI-sparing regimen studied in the setting of therapy optimization can be utilized if no resistance to the agents is present. • Monotherapy with any ARV medication has been associated with drug resistance and higher rates of virologic failure than multidrug ARV regimens; therefore, monotherapy as a switch strategy **is not recommended (AI).** • Discontinuation of HBV antivirals in a person with chronic HBV may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; thus, anti-HBV therapy should not be stopped in people with HBV/HIV **(AII).** • When planning a regimen switch for a person with a history of resistance or intolerance to two or more drug classes, consultation with an HIV specialist is recommended in most cases **(AIII).** • During the first 3 months after an ARV regimen switch, close monitoring is recommended to ensure understanding of the new regimen and to assess adherence, tolerability, safety, and maintenance of 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 nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Key: 3TC = lamivudine; ARV = antiretroviral; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

With currently available antiretroviral therapy (ART), most people with HIV can achieve and maintain HIV viral suppression, the primary goal of HIV treatment. However, people with HIV may need or want to change their antiretroviral (ARV) regimen while virally suppressed for a variety of reasons. When optimizing ART in the setting of viral suppression, several key principles should be considered. The reasons for and principles of ART optimization are discussed below.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To reduce pill burden and/or dosing frequency
- To switch to a regimen with a higher barrier to the development of resistance
- To enhance tolerability and/or decrease short- or long-term toxicity (see Common and/or Severe Adverse Effects Associated with Antiretroviral Medications for a more in-depth discussion of toxicities)
- To prevent or mitigate drug–drug interactions (see the Liverpool HIV Drug Interaction Checker)
- To minimize food requirements or drug–food interactions
- To minimize drug–disease interactions, such as in the setting of renal or cardiovascular disease
- To decrease potential stigma or disclosure concerns (e.g., by switching to long-acting injectable cabotegravir/rilpivirine [LA CAB/RPV])
- To allow optimal use of ART when pregnancy is desired or may occur (see the Perinatal Guidelines)
- To reduce costs borne by the person with HIV and/or to comply with formulary requirements (see Cost Considerations and Antiretroviral Therapy)

General Principles and Considerations for 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 (defined as the inability to maintain suppression of viral replication to HIV RNA levels <200 copies/mL) with the emergence of new resistance mutations, the person may require a more complex and/or less tolerated regimen.

Review Antiretroviral Treatment and Drug-Resistance Histories Before Optimization

Before switching from an effective ARV regimen, it is critical to thoroughly assess a person's full ARV history, including virologic responses, cumulative resistance test results, inferred resistance (as discussed below), and any past ARV-related intolerances, toxicities, or adverse reactions **(AI).**

A review of cumulative resistance test results and clinical and virologic responses to prior regimens is essential when designing a new regimen, especially in people with a history of virologic failure or pretreatment drug resistance. 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. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype, and phenotype 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 re-emerge under the appropriate selective drug pressure.

Resistance can often be inferred from the ARV history. For people with documented virologic failure on a regimen that includes drugs with lower barriers to resistance—such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), lamivudine (3TC), emtricitabine (FTC), elvitegravir (EVG), or raltegravir (RAL)—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 from a regimen with a relatively high barrier to resistance—such as those that include dolutegravir (DTG), bictegravir (BIC), or boosted darunavir (DRV)—to one with a lower barrier to resistance.[1] In most instances, consultation with an HIV specialist is recommended when planning a regimen switch for a person with a history of resistance or intolerance to two or more drug classes **(AIII).**

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA, sometimes called an archived genotype, can be considered for people with viral suppression, particularly if complex or semi-complex pre-existing resistance is suspected. In individuals with no history of virologic failure who are receiving their first or second ARV regimen, or in those with available genotypic resistance results from prior virologic failures, proviral DNA genotypic testing is unlikely to provide additional clinically useful information and **is not recommended (AIII),** even if a baseline genotype is not available.

However, in individuals with a history of multiple virologic failures whose prior ARV treatment history or genotypic resistance test results at the time of virologic failure are unavailable, proviral DNA genotypic testing may be considered **(CIII)**. Results from proviral DNA genotypes should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.[2] Furthermore, it is unclear if all mutations identified are relevant to subsequent regimen selection. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined (see the Drug-Resistance Testing section).

Antiretrovirals No Longer Recommended for Optimization in the Setting of Viral Suppression

The ARV medications nevirapine and oral zidovudine, which can cause serious adverse effects, are no longer recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) and are not suitable for optimizing ART in the setting of viral suppression. Certain protease inhibitors (PIs) (lopinavir and atazanavir [ATV]), first-generation integrase strand transfer inhibitors (INSTIs) (EVG, RAL), and the NNRTI efavirenz also have disadvantages, including higher pill burden, higher rate of toxicity, and, in some cases, a lower barrier to resistance, and therefore are no longer recommended for optimizing ART in the setting of viral suppression. See the What to Start: Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy and What to Start: Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens as Initial Antiretroviral Therapy sections for more detail.

Considerations Regarding Hepatitis B Virus (HBV) and HIV

HBV Screening for People With No History of HBV/HIV Coinfection

People with HIV who are not known to have chronic HBV infection (i.e., not known to have positive hepatitis B surface antigen [HBsAg]) should have HBV serology (HBsAg, hepatitis B surface antibody [anti-HBs], and hepatitis B core Ab [anti-HBc]) performed within 3 months before switching to an ARV regimen that does not include tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF). If a person with HIV shows no evidence of chronic HBV infection (i.e., negative for HBsAg) and is not immune to HBV (i.e., anti-HBs <10 mIU/mL), vaccination should be initiated while

considering the ARV switch (including in those with isolated anti-HBc and those previously vaccinated for HBV). See the HBV Infection and Immunizations for Preventable Diseases sections in the Adult OI Guidelines for details.

Managing People With Chronic HBV Infection (HBsAg Positive)

Tenofovir-based ARV regimens are effective against both HIV and HBV infection. When switching an ARV regimen in a person with HBV/HIV (i.e., HBsAg positive), anti-HBV therapy should be continued and, if feasible, (TDF or TAF) with (3TC or FTC) should be continued as components of the new ARV regimen **(AII).**

There are several effective oral and injectable ARV regimens that do not include tenofovir**.** When using one of these regimens, the HBV treatment options include adding TDF, TAF, or entecavir to the ARV regimen. TDF, TAF, or entecavir may be used as the only HBV-active antiviral in this setting based on their efficacy for the treatment of HBV in people without HIV. TDF or TAF are preferred over entecavir given their higher barrier to HBV resistance. If TAF or TDF cannot be used or it is desired to avoid TAF and TDF, entecavir is the alternative to treat HBV, given together with a fully suppressive ARV regimen **(AII).** Entecavir should not be used in people with HIV without a fully suppressive ARV regimen, given the risk of development of the HIV M184V resistance mutation in this setting.[3] Entecavir **should not be used** in individuals with 3TC-resistant HBV. See Hepatitis B Virus/HIV Coinfection for additional important details regarding entecavir use and dosing for treatment of HBV.

Although 3TC and FTC are active against HBV, the use of 3TC or FTC as monotherapy against HBV infection **is not recommended (AII)** due to the risk of emergent HBV resistance to these drugs.

Discontinuation of HBV antivirals in a person with chronic HBV may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; thus, anti-HBV therapy should not be stopped in people with HBV/HIV **(AII).** Refer to the Hepatitis B Virus/HIV Coinfection section for specific recommendations.

Monitoring After Regimen Switch in People With Positive Anti-HBc and Negative HBsAg

People with HIV and prior exposure to HBV infection (i.e., anti-HBc positive) without evidence of chronic infection (i.e., negative HBsAg) are likely at low risk (<2%) of HBV reactivation and even lower risk of HBV reactivation-associated hepatitis, despite the discontinuation of nucleoside reverse transcriptase inhibitors (NRTIs).[4,5] However, there are no published studies to confidently estimate risk in this population. Within this group, those with positive anti-HBs 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.[6] See more information in the Hepatitis B Virus Infection section in the Adult OI Guidelines.

For people with positive anti-HBc and negative HBsAg who switch to a tenofovir-sparing ARV regimen, alanine aminotransferase (ALT) should be monitored every 1 to 3 months for the first 6 months and every 6 months thereafter, as recommended in the Hepatitis B Virus Infection section of the Adult OI Guidelines. An increase in ALT level 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 of 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 ATV interact with acid-lowering agents, oral absorption of INSTIs can be reduced by the presence of polyvalent cations, and many ARV drugs may interact with drug transporters or drugs that are inhibitors, inducers, or substrates of cytochrome P450 (CYP) enzymes (see the Liverpool HIV Drug Interaction Checker). In addition to new drug interactions, the discontinuation of some ARV drugs may necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may alter the concentration 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 of Pregnancy or Pregnancy Potential

If a woman with HIV is found to be pregnant or desires pregnancy, clinicians should refer to the Perinatal Guidelines for recommendations on ART selection and the safety and efficacy of ARV use at the time of conception and during pregnancy. All pregnancies that occur while a woman is receiving ART should be reported to the Antiretroviral Pregnancy Registry.

Monitoring After Optimizing Antiretroviral Therapy

After a treatment switch, people with HIV should be evaluated closely for 3 months (e.g., monitor for tolerability, viral load for rebound, etc.) **(AIII).** The purpose of this close monitoring is to ensure the person clearly understands their newly prescribed ART regimen, to assess medication tolerance, and to conduct targeted laboratory testing when there are pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if a 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 HIV 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 for the first time, the use of a two- or three-drug ARV regimen (as discussed below) is generally recommended when switching ART in people with suppressed viral loads **(AI). Monotherapy is not recommended (AI)** in the treatment of HIV; this includes monotherapy with either a boosted PI or a second-generation INSTI.[7-10] Both INSTI[11] and boosted PI[12] 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.[13,14]

Optimization Strategies for People With No or Limited Drug Resistance

People who have no history of resistance mutations or virologic failure can likely switch to any two- or three-drug regimen with demonstrated efficacy in people without prior ART experience **(AI)** (see What to Start). In addition, several regimens not used in initial therapy have been studied specifically in the setting of therapy optimization (as discussed below). Several regimens with established efficacy in treatment-naive populations have also demonstrated effectiveness for ART optimization in

people with no or limited resistance, including BIC/FTC/TAF,[15-17] DTG with (TAF or TDF) plus (3TC or FTC),[18] and DTG/3TC (discussed below).

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 viral suppression, particularly when the switch is to a drug with a low barrier to resistance.[1] In the two SWITCHMRK studies, individuals 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 due to underlying NRTI resistance that was not recognized before the switch. In this setting, viral suppression can generally be maintained by switching to drugs with a high barrier to resistance, such as boosted PIs or second-generation INSTIs combined with two NRTIs. However, maintaining viral suppression is less likely when switching 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 no or limited underlying resistance. As discussed earlier, before switching from an effective ARV regimen, it is critical to thoroughly assess a person's full ARV history, including virologic responses, cumulative resistance test results, inferred resistance (as discussed below), and any past ARV-related intolerances, toxicities, or adverse reactions **(AI).**

Within-Class Switches

Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer benefits such as a better safety profile, reduced dosing frequency or pill burden, higher barrier to resistance, or no requirement for PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. In the modern era, common within-class switches include within NRTIs, NNRTIs, and INSTIs. People on older boosted PI-based therapy can also commonly be switched to boosted DRV. When considering a regimen switch in a person with prior virologic failure, switching from a regimen with a high resistance barrier to one with a lower resistance barrier is generally not recommended. Between-class switches, as discussed next, are also commonly utilized in therapy optimization.

Between-Class Switches

Between-class switches (e.g., switching from a boosted PI to an INSTI) are generally safe in people without known resistance. In general, such switches should be avoided if any doubt exists about the activity of the new agent or the other agents in the regimen. In the current era, between-class switches are most common with the NNRTI, PI, and INSTI classes. Other common switches include from therapy containing NRTIs to NRTI-sparing therapy. These switches should also take into consideration, when appropriate, that switching from a high-resistance-barrier medication to a low-resistance-barrier medication, in the setting of prior virologic failure, is generally not recommended as previously discussed.

Two-Drug Oral Regimens

Several two-drug ARV regimens are effective in maintaining HIV virologic control in people who initiated therapy with two- or three-drug regimens and achieved sustained viral suppression for at least 3 months. However, none of these two-drug regimens are effective as treatment for HBV and are therefore **not recommended** for people with HBV coinfection (see the Hepatitis B Virus/HIV Coinfection section). In people with HBV who cannot take TAF or TDF, these regimens can be considered if used with a potent, high barrier–to-resistance 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 to two-drug regimens in people with viral suppression.

Dolutegravir Plus Rilpivirine

Two Phase 3 trials, SWORD-1 and SWORD-2, demonstrated noninferior efficacy of switching to a two-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.[19] Individuals were excluded from the study if they had active HBV infection (unless the person was also on a specific HBV-active agent), 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.[20] 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 three-drug ARV regimen to DTG plus 3TC or FTC as a maintenance strategy in people with ongoing viral suppression and no history of prior virologic failure or resistance to these agents was noninferior to continuing a three-drug regimen in a large randomized clinical trial (TANGO)[21,22] and in multiple smaller clinical trials.[23-28] 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.[29]

Limited prospective and observational cohort data are available on the use of DTG/3TC in people with a history of M184V/I mutations, based either on historical RNA resistance testing and/or proviral DNA resistance testing.[30-33] Although some early data are promising, more clinical outcome data are needed to determine whether specific factors—including duration of pre-switch viral suppression, when the M184V/I was detected, the method of M184V/I detection (i.e., RNA versus proviral DNA genotyping), or other factors—impact the effectiveness of DTG/3TC as a switch strategy in people with HIV with historical M184V/I mutations.[34] Currently, the Panel **does not recommend** the use of DTG/3TC in people with historical M184V/I mutations **(BIII).**

Boosted Darunavir Plus Lamivudine or Emtricitabine

A boosted PI plus 3TC or FTC is a reasonable two-drug optimization option in individuals without resistance who are suppressed on a current regimen and do not have resistance to 3TC/FTC or the boosted PI. Currently, the Panel **does not recommend** the use of a boosted PI with 3TC or FTC in people with historical M184V/I mutations **(BIII).**[35-37] Higher pill burden and potential drug interactions are limitations compared to most of the other two-drug regimens. Boosted DRV is the PI of choice for this combination.[38] Earlier trials supported the use of ATV/ritonavir[39,40] or LPV/r with 3TC.[41] These PIs have a higher pill burden, a higher side effect profile, and are generally less well tolerated than boosted DRV; thus, they are no longer recommended. Individuals with active HBV infection need to be on a potent HBV drug with a high barrier to resistance (e.g., 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.[29]

Boosted Darunavir Plus Dolutegravir

An open-label, Phase 3b, noninferiority clinical trial evaluated a switch to DRV/ritonavir (DRV/r) plus DTG versus the continuation of DRV/r plus two NRTIs; the DRV/r plus DTG regimen was noninferior.[42] Similar results were observed in an observational study of those with NRTI

resistance.[43] The combination of boosted DRV plus DTG can be considered for individuals when resistance or intolerance to NRTIs and/or NNRTIs limits other treatment options. 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). Additional information on the use of boosted DRV plus DTG in treatment-experienced people with ARV resistance is located below (see Data From Virologic Failure Studies Inform Optimization With NRTI Resistance).

Doravirine Plus Islatravir

Doravirine (DOR) in combination with islatravir (ISL), a new NRTI that specifically blocks translocation, has demonstrated efficacy as a switch strategy in two large Phase 3 studies of more than 1,000 people who were virally suppressed without DOR resistance, prior virologic failure, or active HBV infection. In one study, participants switched from BIC/FTC/TAF,[44] and in the other study, individuals switched from a stable two- or three-drug ART regimen.[45] At Week 48, DOR 100 mg/ISL 0.25 mg was noninferior to the baseline regimen for maintenance of viral suppression, with <2% of DOR/ISL-treated participants having HIV RNA ≥50 copies/mL. Contrary to earlier studies with higher doses of ISL, no CD4 T lymphocyte (CD4) cell count or total lymphocyte count declines were noted, and there were no differences in CD4 count changes between treatment arms. Additionally, no differences were observed in weight change between arms in either study. At virologic failure, five of seven individuals on DOR/ISL had no resistance.

The combination of DOR/ISL can be used in people with ongoing viral suppression and no history of prior virologic failure or resistance to DOR or ISL. There are insufficient data to recommend the use of DOR/ISL as a switch strategy in treatment-experienced patients who have known or suspected NRTI and/or NNRTI resistance that could compromise the activity of ISL and/or DOR, including the presence of M184I/V mutations. 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).

Coadministration of DOR/ISL with 3TC or FTC is **contraindicated,** as significant decreases in intracellular islatravir-triphosphate concentrations may occur.[46] DOR/ISL should not be administered with drugs that are strong CYP3A inducers, as significant decreases in DOR concentrations may occur. For detailed information on drug–drug interactions with DOR and/or ISL, see the Liverpool HIV Drug Interaction Checker.

Long-Acting Intramuscular Cabotegravir Plus Rilpivirine

Use of the LA CAB/RPV, administered intramuscularly (IM) every 1 or 2 months, with or without a 28-day or longer oral lead-in with these same agents, is a viable optimization strategy in individuals with HIV viral suppression for at least 3 months.[47-49] Growing data on the use of LA CAB/RPV in the setting of HIV viremia is discussed in the Virologic Failure section. Candidates for LA CAB/RPV should not have known or suspected resistance to either ARV medication. Drug interactions for both the oral lead-in, if used, and the long-term injections need to be considered (see the Liverpool HIV Drug Interaction Checker). 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).

ATLAS and FLAIR were randomized clinical trials with almost 1,200 participants with HIV and viral suppression on oral ART. The studies compared continued oral therapy versus a switch to once-monthly LA CAB/RPV after a 28-day oral lead-in with these same agents.[50,51] In the intention-to-treat analysis, HIV RNA >50 copies/mL at Week 48 occurred in 1.9% of participants in the LA CAB/RPV arms and 1.7% of participants in the oral therapy arms (combining data from both studies), demonstrating that LA therapy was noninferior to continued oral therapy.[47] In ATLAS-2M, every-8-week LA CAB/RPV was noninferior to every-4-week LA CAB/RPV in previously suppressed individuals.[52] In the 687-subject SOLAR study, LA CAB/RPV was noninferior to continued oral

BIC/FTC/TAF. There was no difference in viral suppression with or without oral lead-in when initiating LA CAB/RPV therapy.[53] In the CARES trial, an open-label trial conducted in Africa that enrolled 501 participants, every-8-week LA CAB/RPV was noninferior to continued oral therapy.[54] In all of these studies, virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common.[50,55]

Practical Considerations When Using Long-Acting Injectable Cabotegravir and Rilpivirine

When prescribing LA CAB/RPV, clinicians should refer to the U.S. Food and Drug Administration product label[49] for guidance with practical considerations, including needle length for those with body mass index (BMI) ≤30 kg/m^2 (1.5-inch needle) versus BMI >30 kg/m^2 (2-inch needle), as well as management strategies for planned or unexpected missed doses. HIV viral load monitoring should be performed 4 to 8 weeks after a switch to LA CAB/RPV or when returning to care after missed or delayed doses. When individuals are virally suppressed and continue on schedule with injections, viral load monitoring can then resume per current guidelines (see the Laboratory Testing for Initial Assessment and Monitoring of People With HIV section). Resistance testing, including integrase resistance testing, should be performed in the setting of HIV viremia >200 to 500 copies/mL, regardless of time since last injection.[50-52,56-58]

Initiation of LA CAB/RPV **is not recommended** during pregnancy. Clinicians should refer to the Perinatal Guidelines for recommendations for managing women who become pregnant or are planning pregnancy while receiving LA CAB/RPV. Health care providers are strongly encouraged to register women with HIV who become pregnant while receiving LA CAB/RPV in the Antiretroviral Pregnancy Registry.[50-52,55-58]

Considerations Regarding Long-Acting Cabotegravir Plus Rilpivirine Use in People With a History of Adherence Challenges

There are accumulating data on the use of LA CAB/RPV in people who face challenges with adherence to oral medications. The open-label LATITUDE (ACTG A5359) study enrolled people who had HIV viremia, challenges in taking daily oral ART, and no evidence of CAB or RPV resistance.[59] After adherence support and conditional financial incentives to achieve viral suppression with daily oral ART, participants who were virally suppressed were randomized to monthly LA CAB/RPV or continuing their oral regimen. Of note, despite the requirement for viral suppression before randomization, 24 of the 150 participants randomized to LA CAB/RPV had HIV RNA >200 copies/mL at randomization, including 8 with HIV RNA >10,000 copies/mL. The LATITUDE study was stopped early due to greater efficacy of the LA CAB/RPV regimen. Virologic failure was significantly less common in the LA CAB/RPV group compared to continued oral therapy. See the Virologic Failure section for more discussion on the use of LA CAB/RPV in people with viremia.

Optimization Strategies Specifically in the Setting 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.

When High-Resistance-Barrier Medications Are Available

Results from several clinical trials support or lend theoretical support to optimization strategies for people with viral suppression that include a switch (1) from a low-barrier drug to a high-barrier drug (e.g., DTG, BIC, boosted DRV) or (2) from one high-barrier drug to another in the setting of underlying NRTI genotypic 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, switch to BIC was noninferior to continuing DTG. 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.[60]

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). NRTI resistance was present in 14% of participants, with 10% harboring the M184V/I mutation. 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.[61]

The second-line switch to DTG (2SD) study was conducted at four sites in Kenya in people with HIV who had prior first-line NNRTI plus NRTI regimen failure and achieved viral suppression on an RTV-boosted PI-based regimen without undergoing genotypic resistance testing.[62] In this prospective, open-label trial, 795 participants 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. This study was limited by the absence of genotypic resistance data at the time of NNRTI/NRTI failure. Studies in similar populations have demonstrated that extensive NRTI and NNRTI resistance is expected in this situation, including resistance to 3TC/FTC and tenofovir.[63-65] It is therefore possible to infer that switching from one high-barrier drug to another is safe and effective during viral suppression 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 a high-barrier drug (second-generation INSTI or boosted PI) plus TAF or TDF and FTC or 3TC.[63]

Data From Virologic Failure Studies Inform Optimization With NRTI Resistance

Several studies conducted in resource-limited countries in people with first-line NNRTI-based virologic failure, and who have NRTI resistance, support treatment recommendations for optimizing ART in individuals with NRTI resistance (see the Virologic Failure section for details). In the DAWNING study,[66] which included individuals who were failing 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 to 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 conferring resistance to 3TC and FTC, and 50% having a K65R mutation conferring resistance to TAF and TDF. 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.[63] At Week 96, TDF/3TC was superior to zidovudine/3TC.[67]

Although these were studies of ART use in the setting of initial NNRTI-based virologic failure, the Panel expects 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**,** BIC**,** or boosted DRV (DRV/cobicistat or DRV/r)**.** 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, or to simplify regimens—a regimen with a fully active drug with a high resistance barrier plus two partially active NRTIs can be considered. Both tenofovir (TAF and TDF) and 3TC and FTC may retain partial activity even when resistance is present.

The D2EFT trial evaluated DRV/r plus DTG versus DRV/r plus two NRTIs in people with virologic failure on a first-line NNRTI-based regimen containing two NRTIs. Resistance to one or both NRTIs was common. At 96 weeks, 86% of 251 participants on DTG plus DRV/r achieved viral suppression (viral load <50 copies/mL) with no treatment-emergent resistance observed.[68] Although this study was in the setting of virologic failure, we expect that regimens effective during viremia would also be effective in the setting of viral suppression in people with similar ARV resistance patterns. Several other observational studies have also demonstrated the efficacy of this combination in those with ARV resistance when used in the setting of virologic failure or as treatment optimization in viral suppression.[69-74] The combination of DTG plus boosted DRV can be considered for individuals when resistance or intolerance to NRTIs and/or NNRTIs limits other treatment options. 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).

Optimization Strategies for People With Viral Suppression and a History of Complex Underlying Resistance

Before optimizing the 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, including regimen failures, intolerances, and adverse reactions, as well as review of inferred and cumulative documented drug resistance, should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII).**

As described in the Optimization Strategies Specifically in the Setting 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 maintain suppression in the setting of optimization.[62,63] 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. As noted above, in people who have experienced multiple prior failures and for whom prior ARV history or prior genotypic resistance test results obtained during an episode of virologic failure are not available, proviral DNA genotypic testing may be appropriate **(CIII).** Clinicians should keep in mind that proviral DNA resistance mutations found can be helpful, but some or all archived resistance mutations may not be found with this testing. Previous studies demonstrated that it is best to include at least two (preferably three) 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.[75] 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) or capsid inhibitors (e.g., lenacapavir), recognizing that entry and capsid inhibitors have primarily been studied and are indicated for those with virologic failure.

Knowledge Gaps

- More research is needed on the role of ARV optimization in slowing or reversing excessive ARV-associated weight gain across the age spectrum, from adolescents and young adults to older adults with HIV.
- Research is needed on the long-term virologic outcomes of specific ARV regimens in the setting of underlying viral resistance, such as DTG/3TC or DOR/ISL in people with historical M184V/I mutations.
- Research is needed on the role of the proviral DNA genotype in designing a new regimen in people with unknown ARV history and unknown resistance patterns.
- Research is needed on the safety and efficacy of other novel long-acting optimization strategies.
- More research is needed on managing people with HBcAb positivity after switching to non-HBV-active therapy.
- Research is needed on the safety and efficacy of ART switch strategies for people with chronic kidney disease who are not yet on dialysis.

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Interruption of Antiretroviral Therapy

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Discontinuation or interruption of antiretroviral therapy (ART) may result in viral rebound, increased risk of HIV transmission, immune decompensation, and/or clinical progression.[1-5] Discontinuation **is not recommended** outside the context of a clinical trial **(AI).** However, interruption of ART may occur under certain circumstances, as discussed below. For discussion on the discontinuation of ART in the context of end-of-life palliative care, see HIV and the Older Person. Additionally, for guidance on ART interruptions due to nonadherence, see Adherence to the Continuum of Care.

Management considerations for ART interruptions will depend on regimen type (i.e., oral [PO], long-acting [LA] injectable, or a combination) and factors such as interruption duration, whether interruption is anticipated, and whether effective PO bridging was used for those on LA ART. If interruption of tenofovir (TFV)-containing ART is necessary in people with hepatitis B virus (HBV) and HIV, they should be carefully monitored, because discontinuation of TFV may lead to HBV reactivation and subsequent serious hepatocellular injury (see HBV/HIV Coinfection).

Unplanned Interruption of Oral Antiretroviral Medications

Reasons for short-term interruption (days to weeks) of PO 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 PO ART for a short time (i.e., less than 1–2 days) usually can be done by holding all drugs in the regimen. Whether unplanned interruptions occur by accident (e.g., due to lost medications or interruptions during travel) or by necessity (e.g., due to drug toxicities), all efforts should be made to minimize interruption duration. Recommendations for some specific scenarios are listed below.

When PO ART is interrupted for more than a few days, viral load monitoring should be performed before and after ART resumption as is recommended in people who initiate or modify ART (see Laboratory Testing for Initial Assessment and Monitoring of People With HIV). If viral suppression is not achieved after resuming ART, drug-resistance testing should be performed to assess for emergence of drug resistance and to guide future therapy (see Drug-Resistance Testing).

Unexpected Difficulty Swallowing or Inability to Take Solid Oral Medications

For people with HIV who have difficulty swallowing or require enteral feeding, some ARV drugs are available in liquid or PO powder formulations, and some pills may be crushed. The Oral Antiretroviral/HCV DAA Administration provides information on crushing pills and formulating liquid ARV drugs. Enteral feeds contain polyvalent cations, which may bind and decrease absorption of integrase strand transfer inhibitors (INSTIs)[6]; see the Liverpool HIV Drug Interaction Checker for guidance. Additional information also may be available in drug product labels. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way to continue an effective ARV regimen.

In cases where a person is unable to take medications by any enteral route (e.g., in the context of severe gastrointestinal disease), all components of the PO drug regimen should be stopped simultaneously **(AIII);** after resolution, all components of the ARV regimen should be restarted simultaneously **(AIII).**

Several ARV drugs are available as parenteral formulations; these include intramuscular (IM) cabotegravir plus rilpivirine (CAB/RPV), subcutaneous (SQ) lenacapavir (LEN), intravenous (IV) ibalizumab (IBA), and IV zidovudine (ZDV). The combination of CAB/RPV is approved as a complete regimen for the treatment of HIV (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression). There is limited experience with this regimen as an alternative for people who cannot take PO medications.[7] LEN is not suitable as a bridging option for people who unexpectedly cannot take PO medications because the injectable formulation (without the PO loading doses) would take approximately 4 weeks to reach target concentrations.[8] No data exist on the role of IBA and ZDV in these situations. Clinicians should consult with an HIV specialist before prescribing any of these medications.

Severe or Life-Threatening Toxicity to an Antiretroviral Medication

In the setting of a severe or life-threatening toxicity to an ARV, all components of the ARV drug regimen should be stopped simultaneously **(AIII).** After resolution, a complete regimen that does not include the toxic medication should be started **(AIII).**

Planned or Unplanned Interruption of Long-Acting Injectable Antiretroviral Medications

There may be circumstances in which people who are receiving LA injectable ARV medications (such as CAB/RPV, IBA, or LEN) have delayed or missed injection visits (e.g., due to hospitalization or unexpected travel). Because these agents have extended half-lives, treatment interruptions increase the risk of virologic failure with the development of drug resistance. For anticipated interruptions, PO bridging with suppressive ART should be implemented, and individuals should have a supply of PO ART on hand. Clinical assessment should be performed for unexpected interruptions that occur without PO bridging and/or for people without fully suppressive PO ART options. Some individuals may be receiving a regimen that contains both PO and LA injectable ARVs; if an interruption in the PO components of the ARV regimen occurs, see Unplanned Interruption of Oral Antiretroviral Medications above.

LA CAB/RPV is approved as a complete regimen given once monthly or every 2 months for the treatment of HIV. If LA CAB/RPV injections will be missed or delayed by >7 days, suppressive PO bridging ART should be started within 1 week (+/- 7 days) of the next scheduled injection. PO bridging may be comprised of PO CAB plus PO RPV, or another fully suppressive ARV regimen (e.g., dolutegravir/RPV or a prior well-tolerated and effective regimen). PO bridging should be continued until LA CAB/RPV injections are restarted. If the injections are missed or delayed by >7 days without PO bridging, the person with HIV should be clinically assessed to determine whether resumption is appropriate. See the prescribing information for dosing guidance after missed or delayed injections.[9] If discontinuing LA CAB/RPV, transition to a suppressive PO ARV regimen should occur within 1 to 2 months of the last IM doses, depending on the dosing schedule. Plasma viral load testing should be performed before the transition, and drug-resistance testing should be considered if plasma viremia is present.

People with drug-resistant HIV may receive IBA or LEN as a component of a subsequent regimen. People who have interruptions of the LA agent and/or PO background regimen should be assessed to determine whether resumption is appropriate. Plasma viral load testing should be performed; see Drug-Resistance Testing for information regarding IBA and LEN resistance testing. The recommended reinitiation strategies are described below.

IBA is initiated with a 2,000-mg IV loading dose, followed by 800 mg IV every 14 days as maintenance therapy. If a dose is missed by ≥3 days, a repeat loading dose of 2,000 mg IV is recommended as soon as possible before resumption of maintenance therapy.[10]

After an initial PO and SQ loading phase, LEN is given as two SQ injections every 6 months (26 weeks). If a dose is missed by >2 weeks (i.e., >28 weeks from the last injection), PO LEN 300 mg once weekly should be given for up to 6 months until the injections can be resumed. If a lapse of >28 weeks occurs between injections without LEN PO bridging, individuals should be reassessed clinically for appropriateness of continuation. If LEN is to be continued, therapy should be reinitiated with PO and SQ loading doses as recommended in the prescribing information.[11]

Analytical Treatment Interruption of Antiretroviral Medications in a Research Setting

Several research studies are evaluating approaches to achieve sustained ART-free viral remission or a functional cure for HIV.[12] 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.[13] 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 of conducting these clinical trials safely.[14] To date, ATI trials have only enrolled people who received daily PO ART. Currently, no published data exist on strategies for ATI in people receiving LA injectable ARV medications.

Before ART is interrupted, participants in ATI trials should be made aware of and understand the risks of viral rebound,[15] acute retroviral syndrome, increased HIV transmission risk, CD4 T lymphocyte cell count decline, HIV disease progression, minor HIV-associated manifestations (e.g., oral thrush) or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), drug resistance development, and potential psychosocial effects of ATI.[14] Participants 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.

When the ARV regimen contains PO drugs with different half-lives, stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life. However, limited to no data exist on optimal discontinuation strategies in the context of contemporary ART, including with nucleoside reverse transcriptase inhibitors that have longer intracellular half-lives (e.g., TFV, emtricitabine),[16,17] ARV medications with higher genetic barriers to resistance, or currently available coformulated regimens.

Knowledge Gaps

- Research is needed to identify optimal parenteral ARV regimens to use in people with difficulty swallowing or who are unable to take medications by any enteral route.
- Research is needed on best practices for supporting PO bridging of LA injectable ART during treatment delays or interruptions.
- Research is needed on the safety and risks of ATIs, including safe interruption of LA injectable ARVs and contemporary ART.

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CARDIOVASCULAR AND METABOLIC COMPLICATIONS IN PEOPLE WITH HIV

Introduction

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With continuous antiretroviral therapy (ART) and viral suppression, life expectancy for people with HIV is approaching that of people without HIV. Despite a narrowing mortality gap between people with and without HIV, some estimates suggest a gap of up to 10 years, which remains clinically relevant.[1] With prolonged survival, age-related comorbidities have increased at higher rates among people with HIV than among those without HIV, including atherosclerotic cardiovascular disease, metabolic complications (e.g., weight gain, insulin resistance, dyslipidemia, and metabolic syndrome), cancer linked to pro-oncogenic viruses, and other aging-related conditions.[2-8] Three key factors that contribute to this burden of age-related noncommunicable diseases among people with HIV include: (1) an over-representation of traditional risk factors in this population, especially higher rates of smoking, diabetes, and dyslipidemia; (2) possible cardiometabolic toxicities from some antiretroviral drugs; and (3) HIV-associated chronic inflammation and immune activation, which are not completely abated by suppressive ART.[9-18]

In this context, the U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents has developed this section to provide guidance on the prevention and optimal management of cardiovascular disease (CVD) and metabolic complications in people with HIV. This section is divided into four subsections: (1) HIV-associated inflammation and immune activation as a contributor to CVD and metabolic complications, (2) CVD risks among people with HIV, and (3) weight gain among people with HIV receiving ART. Given the relevance of HIV-associated immune activation and inflammation as a mediating factor across the comorbidities discussed, this topic is also included within this section of the guidelines.[19-24]

Other important CVD manifestations and metabolic complications are not currently covered in detail here, such as insulin resistance and risk for diabetes mellitus, metabolic syndrome, metabolic dysfunction–associated steatotic liver disease, heart failure, sudden cardiac death, and bone disease. At this time, guidance on the management of these conditions remains similar for people with and without HIV infection. Still, these conditions represent areas of active research, and as future evidence arises that informs management specific to people with HIV, this section may be expanded.

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Immune Activation and Inflammation Among People With HIV Receiving Antiretroviral Therapy

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Key Considerations and Recommendations
• HIV-related immune activation and systemic inflammation, despite viral suppression with antiretroviral therapy, are associated with increased risk for cardiovascular disease and metabolic complications, as well as a broad spectrum of comorbidities. • Switching or adding antiretroviral (ARV) drugs solely to reduce immune activation or inflammation **is not recommended,** except in a clinical trial **(AII).** • The use of immunomodulatory or anti-inflammatory therapy to reduce HIV-related immune activation or inflammation **is not recommended,** except in a clinical trial **(AII).** • Routine monitoring of markers of immune activation or inflammation (e.g. high-sensitivity C-reactive protein [CRP] or interleukin-6 [IL-6]) to inform the clinical management of HIV **is not recommended (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*

The Influence of Immune Activation and Inflammation on Disease Risk in People With HIV

Compared to people without HIV, people with HIV have demonstrated higher overall immune cell activation and higher levels of systemic inflammation (as measured by biomarkers such as interleukin-6 [IL-6]) and acute phase reactants (e.g., high-sensitivity C-reactive protein [hsCRP]).

Although immune activation declines with suppressive antiretroviral therapy (ART), it often persists at elevated levels in virologically suppressed people with HIV.[1,2] Extensive literature over the past decades has demonstrated a link between HIV-related systemic inflammation and an increased risk of age-related comorbidities, as well as mortality from non-AIDS conditions.[3-16] Specifically, blood markers of systemic inflammation among people with HIV have been associated with increased risk for a wide range of chronic conditions, including atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, obesity, cancer, osteopenia/osteoporosis, and chronic obstructive pulmonary disease.[8-18] Even in individuals with CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3, immune activation and inflammation are associated with increased morbidity and mortality from age-related comorbidities.[19,20]

Antiretroviral Therapy as a Strategy to Reduce Inflammation

Early HIV diagnosis combined with prompt ART initiation can effectively achieve a lower level of persistent immune activation. Most inflammatory markers decline during the first several months of ART and may achieve a stable "setpoint" within 1 to 2 years.[21,22] 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.[23] These data reinforce the recommendation to start ART as soon as possible after HIV diagnosis, regardless of CD4 count (see Initiation of Antiretroviral Therapy).

Currently, data do not support intensifying or modifying ART as a strategy to reduce immune activation after viral suppression is already achieved. For example, adding antiretroviral (ARV) drugs to an already suppressive regimen (or ART intensification) does not consistently improve immune activation.[24-28] 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, these studies have limitations, and results are not consistent across markers or among studies.[29-31] Thus, adding or switching ARVs solely to reduce immune activation or inflammation **is not recommended,** except in a clinical trial **(AII).**

Adjunct Treatments to Reduce Immune Activation and Inflammation

Treatment strategies targeting immune activation and inflammation have been a focus of ongoing investigation. In this context, research strategies to mitigate inflammation among people with HIV on suppressive ART have typically taken one of three approaches: (1) target the root drivers of immune activation specific to HIV disease, (2) downregulate inflammatory pathways broadly, or (3) leverage anti-inflammatory properties of medications targeting traditional risk factors.

The HIV-related mechanisms driving immune activation have been posited to include viral persistence, permanent injury impairing immune recovery (i.e., due to lymphatic tissue fibrosis), presence of copathogens, as well as dysbiosis and microbial translocation.[32-36] Among these mechanisms, investigational approaches have targeted HIV reactivation from latently infected cells, fibrotic pathways, the gut microbiome, and cytomegalovirus coinfection.[27,37-41] However, thus far, none of these strategies have improved clinical outcomes. Therefore, these interventions should be pursued only in the context of clinical trials.

Data have emerged demonstrating the potential clinical benefit of broadly anti-inflammatory and immunosuppressive strategies among people without HIV who are at high risk for ASCVD events. The CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) studied canakinumab, a human monoclonal antibody targeting cytokine interleukin-1b, a driver of the IL-6 signaling pathway, as a secondary prevention strategy among people with known ASCVD who do not have HIV. CANTOS demonstrated a treatment effect for reducing inflammation, as well as cardiovascular events and cancer death, in the general population.[42] In people with HIV, canakinumab and tocilizumab, inhibitors of the receptor for IL-6, have been shown to reduce blood levels of markers of inflammation and immune activation.[43,44] However, it is unclear whether the potential risks of these immunomodulatory therapies, including the increased sepsis risk seen in the CANTOS trial,[42] outweigh their possible benefits for people with HIV, particularly with long-term use. Therefore, the clinical use of immunomodulatory or anti-inflammatory therapy solely to reduce HIV-associated immune activation or inflammation **is not recommended** among people with HIV, except in a clinical trial **(AII).**

Finally, beyond the well-established clinical benefit for reducing ASCVD events, hydroxymethylglutaryl coenzyme A (or HMG-CoA) reductase inhibitors, also known as statins, have been shown to improve biomarker levels of inflammation (e.g., hsCRP) and immune activation in the general population.[45,46] In this context, data from REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) have demonstrated a reduction in cardiovascular events with pitavastatin use among people with HIV (see Statin Therapy in People With HIV). Other commonly used medications with anti-inflammatory properties—such as aspirin, angiotensin-converting enzyme inhibitors, methotrexate, and angiotensin receptor blockers—have failed to consistently reduce biomarkers of immune activation and/or inflammation in people with HIV in randomized controlled trials.[39,47-50]

Monitoring Inflammation

As evidence is insufficient to inform differential screening practices or clinical management strategies (e.g., for ASCVD) based solely on the level of individual blood biomarkers, there is no clear rationale to routinely monitor levels of immune activation and inflammation in people with HIV. Thus, routine monitoring of markers of immune activation or inflammation (e.g., hsCRP, IL-6) to inform the clinical management of HIV **is not currently recommended (BII).**

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Cardiovascular Complications in People With HIV

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Key Considerations and Recommendations
Antiretroviral Management
• All people with HIV should maintain viral suppression with continuous antiretroviral therapy (ART) to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) **(AII).**
• Due to concerns regarding an increased risk of cardiovascular events, alternative antiretroviral (ARV) medications should be considered in place of abacavir and lopinavir/ritonavir in people with higher underlying ASCVD risk or known ASCVD **(AII).**
ASCVD Risk Stratification
• For people with HIV aged 40–75 years, 10-year ASCVD risk score should be calculated using the Pooled Cohort Equations (or PCE) at least annually to inform management, including whenever lipids are measured or in certain clinical scenarios that may affect ASCVD risk* **(BIII)** (see Atherosclerotic Cardiovascular Disease Risk Scores in the text).
• Lipid screening should be performed in people with HIV **(AIII),** with the following suggested frequency: (1) at entry into care or at the time of ART initiation, (2) 3–6 months after ART initiation once viral suppression is achieved, (3) annually for those aged ≥40 years or receiving statin therapy, (4) every 1–3 years for those aged <40 years **and** not on statin therapy, and (5) with changes in cardiovascular disease (CVD) risk factors (see text for additional details on monitoring).
• There is insufficient evidence to support the use of inflammatory biomarkers for ASCVD risk stratification among people with HIV.
• When compared to the general population, women with HIV have both a greater increase in relative risk of ASCVD and a greater underprediction of ASCVD by risk scores than men with HIV. For women with HIV, it is critical to ensure optimal ASCVD risk factor modification regardless of ASCVD risk score, implement ASCVD prevention strategies, and perform diagnostic evaluation if they present with possible cardiac symptoms.
ASCVD Prevention and Risk Factor Management
• Statin therapy is recommended for all people with HIV aged 40–75 years and in additional clinical scenarios for other age groups to reduce the risk of ASCVD and major adverse cardiovascular events. See Statin Therapy in People With HIV for recommendations on statin use.
• The use of immunomodulatory therapy to reduce HIV-associated ASCVD risk **is not recommended** except in a clinical trial **(AII).**
• Some drugs prescribed to prevent or treat CVD may have clinically significant interactions with certain ARV drugs. Before initiating or changing ARV drugs or concomitant medications, clinicians should carefully assess for potential interactions **(AIII).**
• All people with HIV should be counselled about ways to reduce CVD risk through behavioral modifications such as healthy diet, weight control, regular exercise, smoking cessation, and limiting alcohol consumption.
• Optimal management of comorbidities (e.g., hypertension, diabetes, obesity) remains important to further reduce CVD risk among people with HIV.
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-related CVD risk-enhancing factors include prolonged duration of HIV infection, delayed ART initiation, long periods of HIV viremia and/or treatment nonadherence, low current or nadir CD4 T lymphocyte cell count (e.g., <350 cells/mm^3), exposure to some older ARV drugs associated with cardiometabolic toxicity, and/or coinfection with hepatitis C virus.

Overview

Most people with HIV who are using continuous antiretroviral therapy (ART) and achieve viral suppression have a life expectancy that is approaching that of people without HIV.[1] However, a gap in mortality remains due to comorbidities such as atherosclerotic cardiovascular disease (ASCVD). As mortality from AIDS events among people with HIV has declined, the proportion of ASCVD-related deaths has increased. When compared to people without HIV, people with HIV have an approximately twofold higher risk of developing ASCVD, even after accounting for traditional cardiometabolic risk factors.[2] The age at incident ASCVD diagnosis among people with HIV is often younger than that of people without HIV. In this context, the 2018 Multisociety Cholesterol Guidelines identified HIV as an ASCVD risk enhancer.[3] Factors influencing ASCVD risk among people with HIV include a higher prevalence of traditional cardiometabolic risk factors compared with the general population,[4] ongoing systemic inflammation associated with HIV despite viral suppression,[5] and cardiometabolic toxicity associated with certain ARV drugs.[6,7] Data also suggest that excess ASCVD risk relative to the general population is greater among women with HIV than among age-matched men with HIV.[8,9] In addition, differential access to screening and treatment of ASCVD risk factors also contributes to excess ASCVD risk among certain people with HIV in the United States.[10,11]

While there has been extensive focus on the epidemiology and pathogenesis of ASCVD among people with HIV, there are also data demonstrating increased risk of other cardiac and vascular diseases. People with HIV have an increased risk of developing stroke (including ischemic and hemorrhagic), heart failure, arrhythmia or sudden cardiac death, and thrombosis.[12-15] Risk factors for these outcomes are thought to be similar to those for ASCVD, with an etiologic role for both traditional risk factors and HIV-related factors. Currently, this section of the guidelines is focused on primary prevention strategies for people with HIV, with an emphasis on ASCVD. As data emerge concerning primary and secondary prevention strategies for other cardiovascular outcomes specific to people with HIV, this section may be expanded.

HIV-Related Risk Factors for Atherosclerotic Cardiovascular Disease

Factors related to HIV and its treatment have been shown to be important contributors to excess cardiovascular disease (CVD) risk. Specifically, HIV-related inflammation has been associated with elevated CVD risk. This inflammation is increased in the presence of active viremia and decreases with ART, but still remains elevated when compared to those without HIV (see Introduction). Data from the SMART trial demonstrated that continuous ART not only improves HIV-related outcomes but also significantly reduces non-AIDS events, including CVD, an observation thought to be related to the beneficial effects of ART on inflammation.[16] In the large Veterans Aging Cohort Study (VACS), myocardial infarction (MI) risk was independently associated with detectable or increased HIV RNA; compared to people without HIV, MI risk was increased by 39% in those with HIV RNA <500 copies/mL and by 75% in those with HIV RNA ≥500 copies/mL.[17] In REPRIEVE, even low-level HIV viremia (median 62 copies/mL) was linked to increased rates of major adverse cardiac events (MACE), as viremic individuals had a higher risk than those with viral load below the limit of detection (adjusted hazard ratio 1.4; 95% confidence interval, 1.00–1.97)[4,18]; however, another recent study did not show an association between HIV viremia and CVD.[19] Based on these findings, continuous ART is recommended for all people with HIV to maintain viral suppression and reduce ASCVD risk **(AII).** Immunomodulatory therapy as an intervention to reduce HIV-associated ASCVD risk **is not recommended** except in a clinical trial **(AII).** See Immune Activation and Inflammation Among People With HIV Receiving Antiretroviral Therapy for additional details.

Additional factors related to HIV may further impact ASCVD risk. Lower CD4 T lymphocyte (CD4) cell count and nadir CD4 count have been shown to be associated with CVD events independent of traditional CVD risk factors or specific ART,[20,21] with VACS demonstrating CD4 <200 cells/mm^3 as

an independent predictor of MI with an increased risk of nearly 90%.[17,22] HIV-related CVD risk-enhancing factors include prolonged duration of HIV infection, delayed ART initiation, long periods of HIV viremia and/or treatment nonadherence, low current or nadir CD4 count (e.g., <350 cells/mm^3), exposure to older antiretroviral (ARV) drugs associated with cardiometabolic toxicity, and coinfection with hepatitis C.[23]

Women with HIV have also been shown to have a greater relative risk of ASCVD compared to men with HIV. Although data indicating the absolute risk of MI is similar between genders—12.71 versus 10.48 per 1,000 person-years for women and men with HIV, respectively—women with HIV have exhibited a nearly 3- to 4-fold increase in relative MI risk versus a 1.5- to 2-fold increase for men compared to sex-specific rates among people without HIV.[9,24-26] A substudy from REPRIEVE demonstrated the absence of an expected protective effect of female sex for the development of a MACE.[4] The presence of HIV-related ASCVD risk-enhancing factors, including female sex, may strengthen the rationale for ASCVD prevention strategies, including statin initiation (see Statin Therapy in People With HIV), and may be used to inform decisions to avoid certain ARV medications that have been associated with increased ASCVD risk.

Antiretroviral Therapy and Cardiometabolic Complications

Specific ARV medications and classes have been associated with potential cardiometabolic toxicity, which has informed the U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations on ART regimen selection to reduce risk for cardiometabolic complications. See Interactions Between ARV Drugs and Drugs for Treatment or Prevention of Cardiovascular Diseases below and Table 7 of What to Start for more information. Specifically, for individuals with elevated traditional ASCVD risk or known CVD, the selection of an ART regimen should consider options that minimize the introduction of new cardiometabolic adverse effects.

Antiretroviral Therapy and Atherosclerotic Cardiovascular Disease Risk

Individual ARV medications and classes have been linked to increased risk of CVD events. An association between abacavir (ABC) use and MI was first reported in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, with the increased risk noted only with recent/current ABC exposure (i.e., within 6 months) and particularly among participants with pre-existing cardiac risk factors.[27] Since the D:A:D report, multiple studies, systematic reviews, and meta-analyses have evaluated the relationship between ABC therapy and cardiovascular events, with some confirming the initially observed association and others failing to identify an association.[27-32] Retrospective analyses from the REPRIEVE study corroborated the D:A:D results, showing an increased hazard of a first MACE with ART regimens, including ABC versus tenofovir-containing regimens,[33] and an increased MACE hazard of 62% in participants with previous use and 41% with current use of ABC compared with participants who were never exposed.[34] An association between ABC and ASCVD risk reported in multiple large studies provides a rationale to consider underlying ASCVD risk when using ABC as a component of ART. Based on these data, the Panel recommends considering alternative ARV medications in place of ABC in people with HIV and higher underlying ASCVD risk or known CVD **(AII).**

An early study from the D:A:D cohort demonstrated a 16% increased risk of MI per year of cumulative protease inhibitor (PI) exposure,[35] specifically with older PIs (e.g., indinavir and ritonavir-boosted lopinavir [LPV/r]). A case-control study within the French HIV ANRS cohort CO4 also found a 33% increase in MI risk with LPV/r use.[36] A later study from the D:A:D cohort showed a 59% increased risk of CVD per 5 additional years of use with ritonavir-boosted darunavir (DRV/r) but not ritonavir-boosted atazanavir (ATV/r),[37] yet subsequent studies did not observe an association between boosted darunavir and increased CVD risk.[38-40] Based on these data, the Panel

recommends considering alternative ARV medications in place of LPV/r in people with HIV and higher underlying ASCVD risk or known CVD **(AII).** If use of DRV/r is indicated, clinicians should weigh the potential benefits of therapy versus the potential cardiovascular risk.

The effect of integrase strand transfer inhibitors (INSTIs) on the risk of CVD is an area of active research, with recent studies showing inconsistent results. In a multicenter observational study of the international RESPOND consortium, INSTI exposure was associated with a nearly twofold greater incidence of a composite CVD endpoint within the first 6 months after exposure compared to no INSTI exposure,[41] and the increased risk persisted throughout the first 24 months. Subsequently, two target trial emulation studies found no association between INSTI use and a composite CVD outcome that included MI, stroke, or invasive cardiovascular procedures, regardless of previous ART experience.[42,43] Based on current data, there is insufficient evidence to recommend modifying suppressive INSTI-based ART regimens in people with weight gain, higher underlying ASCVD risk, or known CVD.

Antiretroviral Therapy and Dyslipidemia

Higher levels of low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides have been observed with tenofovir alafenamide (TAF), efavirenz (EFV), all boosted PIs, and elvitegravir/cobicistat (EVG/c).[44,45] Among the PIs, similar lipid changes have been shown in participants from a randomized trial of ATV/r- and DRV/r-based regimens.[46] Importantly, differences in lipid levels between two ART regimens can be due to a lipid-raising effect of a given medication and/or a lipid-lowering effect of the other medication. For example, levels of total cholesterol, LDL, HDL, and triglycerides are higher in participants who received TAF when compared with those who received tenofovir disoproxil fumarate (TDF) in multiple randomized controlled trials.[47,48] However, data from a placebo-controlled pre-exposure prophylaxis trial support that TDF exposure has an independent lipid-lowering effect (for total cholesterol, LDL, and HDL).[49] Further, data support that total cholesterol to HDL ratios did not differ between participants receiving TAF and those receiving TDF,[50,51] and the clinical significance of CVD risk from increases across all lipid indices without changes in total to HDL ratios is uncertain.

Antiretroviral Therapy and Diabetes/Insulin Resistance

Direct effects on diabetes mellitus (DM) and insulin resistance have been observed with older ARVs, including ZDV and LPV/r.[52] Several studies have demonstrated an increased risk of DM with INSTI use,[53-55] an association that may be mediated in part by weight gain.[56] An association between ART and DM has not been consistently observed with other contemporary ARVs, including those recommended as initial therapy in the guidelines.

Antiretroviral Therapy and Other Cardiac Complications

EFV, as well as higher than recommended doses of fostemsavir and rilpivirine, have been associated with QTc (QT corrected for heart rate) prolongation.[57-59] These ARV drugs should be used with caution in people with pre-existing heart disease, QTc prolongation, or concomitant use of medications that may increase drug concentration or prolong the QTc interval. Both ATV/r and LPV/r have been associated with PR prolongation, particularly among people with risk factors, including pre-existing heart disease and concomitant use of medications that may cause PR prolongation.[60,61]

Strategies for Atherosclerotic Cardiovascular Disease Risk Estimation and Screening For People With HIV

Cardiovascular risk assessment and prevention strategies developed for the general population do not reflect HIV-specific factors, such as inflammation and immune activation or potential

contributions from certain ARV drugs, which are key mechanistic contributors to HIV-associated CVD. This section will address ASCVD risk estimation and lipid screening for people with HIV. ASCVD prevention strategies specific to people with HIV are further discussed in the Introduction and Statin Therapy in People With HIV sections.

Lipid Monitoring

Lipid screening should be performed in people with HIV **(AIII),** given the increased risk for ASCVD and the increased rate of dyslipidemia associated with certain ARV drugs. A fasting or random lipid profile should be obtained for all people with HIV at entry into care or at the time of ART initiation or modification. If a random profile is abnormal, a fasting lipid profile should be obtained. Lipid levels should be rechecked 3 to 6 months after starting ART or later if viral suppression is not achieved within 6 months. Lipid levels measured after initiation of ART should then be used to calculate an ASCVD risk score and determine indications for statin therapy (see Statin Therapy in People With HIV). Among people with HIV who are aged 40 years or older or who are any age and are receiving statin therapy, lipid monitoring should be performed annually to reassess ASCVD risk and inform decisions on statin management and/or other risk modification strategies. Further, specific to people on statin therapy, the approach to monitor lipids at least annually to assess adherence and the need for treatment intensification is consistent with recommendations by the *2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guideline on the Management of Blood Cholesterol* among people in the general population.[62] For people with HIV who are under age 40 and not receiving statin therapy, lipid levels should be monitored every 1 to 3 years to reassess ASCVD risk. For all people with HIV, lipid monitoring may occur more frequently based on lifestyle factors or clinical scenarios, including changes in traditional ASCVD risk factors (e.g., weight gain, new diagnosis of hypertension, concomitant medications that affect lipids, or change to an ARV regimen with increased ASCVD risk).

Atherosclerotic Cardiovascular Disease Risk Scores

ASCVD risk prediction algorithms enable clinicians to quantify the risk of a future cardiovascular event and are used in clinical practice to stratify risk and to guide the intensity of ASCVD preventative measures and risk factor management, including statin use and antihypertensive therapy. Yet established ASCVD risk prediction scores validated in the general population typically do not include risk factors specific to HIV, and they have been shown to systematically underestimate risk among people with HIV. Data from multiple studies and a meta-analysis have shown that the ACC/AHA Pooled Cohort Equations (PCE) underpredict ASCVD risk in people with HIV in high-income countries.[63-68] Studies also suggest the accuracy of established ASCVD risk scores for people with HIV may vary by patient demographics and clinical characteristics, with underprediction of ASCVD risk demonstrated among women,[63,66,67] Black or African-American individuals,[63,67] and individuals with low or moderate predicted CVD risk versus high risk.[63,65,66] ASCVD risk score accuracy may also differ by region globally, with a study of REPRIEVE data showing underprediction of risk in high-income countries yet overprediction in low-income and middle-income countries.[67] Additional research is needed to better tailor ASCVD risk scores to people with HIV overall, as well as by geographic region and demographic and clinical characteristics.

In 2023, the AHA developed a new set of ASCVD risk equations for the general population. The Predicting Risk of CVD EVENTs (PREVENT) equations differ from the PCE on several levels, including the inclusion of a new derivation dataset of more than 6 million individuals, new variables reflecting a broader cardiovascular-kidney-metabolic framework, a new outcome including heart failure, and the removal of race from the models.[69] Because PREVENT was developed for the general population, this updated risk score does not incorporate risk factors specific to HIV or its treatment. Predicted ASCVD risk has been shown to be lower using PREVENT in the general population.[70] For people with HIV,[71] 97% had a lower predicted risk, and 58% fewer would be

strongly recommended for statins using the PREVENT (vs. PCE) risk score. Further study is needed to determine if and how the PREVENT risk estimates may inform the clinical management of people with HIV.

The PCE is recommended for predicting ASCVD risk among people with HIV, as it has been more extensively studied in this population and used in the REPRIEVE trial to inform recommendations on the use of statins in people with HIV (see Statin Therapy in People With HIV). For people with HIV aged 40 to 75 years, the 10-year ASCVD risk score should be calculated using the PCE at least annually, including whenever lipids are measured or in certain clinical scenarios that may affect ASCVD risk (e.g., changes in traditional CVD risk factors, such as weight gain, new diagnosis of hypertension, concomitant medications that affect lipids, or change to an ARV regimen with increased ASCVD risk) **(BIII).** Presently, there is insufficient evidence to recommend strategies to account for the underprediction of ASCVD risk by the PCE and other established ASCVD risk scores among people with HIV, including use of inflammatory biomarkers.

Interactions Between Antiretroviral Drugs and Drugs for Treatment or Prevention of Cardiovascular Diseases

People with HIV may receive a statin to prevent ASCVD or medications for the treatment of CVD risk factors or underlying CVD. Some of these drugs may have clinically significant interactions with some ARV drugs. Before initiating or changing these medications, clinicians should carefully assess for potential interactions **(AIII).** The Liverpool HIV Drug Interaction Checker provides guidance for managing these interactions. Major mechanisms of pharmacokinetic (PK) interaction between ARV drugs and cardiac drugs are noted in the sections below.

Cytochrome P450 Enzymes

Many cardiac drugs (such as certain antiarrhythmics, anticoagulants, beta-blockers, calcium channel blockers, statins, and others) are substrates of cytochrome P450 (CYP) enzymes and may interact with ARV drugs that are inhibitors or inducers of these enzymes. Concomitant use with:

- CYP inhibitors (such as the PK boosters ritonavir and cobicistat, and the capsid inhibitor lenacapavir) may—
    - Increase the systemic exposure and potentially toxicities of cardiac drugs that are CYP substrates
    - Decrease the efficacy of the antiplatelet drug clopidogrel (a prodrug) by inhibiting the formation of its active metabolite
- CYP inducers (such as EFV and etravirine) may—
    - Reduce concentrations and efficacy of the cardiac drugs that are CYP substrates

Drug Transporters

Interactions related to drug transporters may also play a role in drug disposition. For example, the INSTIs bictegravir, dolutegravir, and elvitegravir are inhibitors of organic cation transporter 2 (OCT2) and may reduce renal elimination of certain antiarrhythmics (such as dofetilide and disopyramide), thereby increasing concentrations of the cardiac drug and the risk for adverse events.

Because some interactions may result in serious toxicities or lack of efficacy, certain drug combinations are not recommended or are contraindicated. In these cases, clinicians should assess if alternative ARV drugs and/or alternative cardiac drugs can be used. In other cases, dosage modification and therapeutic drug monitoring of cardiac drugs may be needed to guide therapy, with close follow-up to assess efficacy and potential toxicity.

Management of Comorbidities and Traditional Cardiovascular Disease Risk Factors

Although HIV-specific factors influence CVD risk, traditional risk factors also play an important role among people with HIV. Although factors such as advancing age and other demographic characteristics cannot be changed, many CVD risk factors are modifiable with behavioral and pharmaceutical interventions. The AHA has outlined eight components of cardiovascular health for everyone: healthy diet; participation in physical activity; avoidance of nicotine; healthy sleep; healthy weight; and healthy levels of blood lipids, blood glucose, and blood pressure.[72]

Traditional CVD risk factors predict incident CVD events and occur at higher rates among people with HIV compared with the general population.[4] A 2025 global meta-analysis assessed common CVD risk factors among people with HIV and found higher odds of CVD incidence associated with DM, hypertension, dyslipidemia, smoking, and a prior history of CVD.[73] A U.S. population-based study among people with HIV found conventional risk factors, such as tobacco use, hypertension, and obesity, to be persistently associated with CVD incidence over follow-up periods for as long as 15 years.[74] Nontraditional risk factors for CVD that are not specific to HIV, including alcohol use disorders, depression, and hepatitis C virus coinfection, are also more common in people with HIV.

The aforementioned data highlight the importance of preventing and managing traditional risk factors among people with HIV. A longitudinal study comparing CVD risk factors among people with and without HIV found that associations between CVD and HIV status were attenuated when dyslipidemia and DM were well controlled.[75] Recommendations for screening and management of CVD risk factors are outlined in the HIVMA/IDSA 2024 update, *Primary Care Guidance for Providers Who Care for Persons With Human Immunodeficiency Virus*.[76] For women with HIV, ensuring optimal CVD risk factor modification regardless of CVD risk score and performing diagnostic evaluation for possible cardiac symptoms is critical given the greater relative risk of ASCVD.

Other Management Considerations and Unanswered Questions

Estrogen, Progestins, or Testosterone Therapy and Cardiovascular Risk

Studies have produced conflicting results on associations between estrogen, progestins, or testosterone therapy and CVD risk, varying by study design, study population, duration and timing of therapy, and other clinical factors.[77-80] Research on relationships between these drugs and CVD among people with HIV is even more limited.[81-84] Data on testosterone use among people with HIV have been limited to the treatment of testosterone deficiency and lack longitudinal information on CVD-related outcomes.[85,86] Studies of estrogen use suggest a potential increase in CVD risk; however, this association may vary by dose, mode of delivery, and underlying physiological stress.[79-81,87] A longitudinal study of combined estrogen and progestin use for oral contraception among people with HIV suggested increased CVD risk, though the association was not statistically significant.[88]

As the population with HIV ages, a growing number of women with HIV are entering menopause. CVD is the leading cause of morbidity and mortality in menopausal women, and this risk is increased in women with HIV.[89,90] Studies of the cardiovascular risk associated with menopausal hormone therapy have led to changes in guidelines over the years.[90] Systemic hormone therapy is not currently recommended for CVD prevention or treatment.[91] However, hormone therapy remains the most effective treatment for vasomotor symptoms.[92] Some research suggests that women with HIV are undertreated for menopausal symptoms.[93] However, data are lacking on menopause and hormone therapy in women with HIV, including whether menopause amplifies the effects of HIV on

CVD risk.[94] Current HIV primary care guidelines recommend that menopause-related hormone therapy for women with HIV should not differ from the care of women without HIV.[76]

Cardiovascular Risks of Adults Who Acquired HIV Perinatally or During Adolescence

An increasing number of adults acquired HIV perinatally or during adolescence, but the cardiovascular effects of perinatal or adolescent HIV acquisition and long-term ART use are unclear. For individuals who acquired HIV perinatally, it is hypothesized that exposure to HIV and ART *in utero* while the cardiovascular system is developing, use of older ART drugs with cardiometabolic and mitochondrial toxicity, lifelong duration of infection, and a longer period of chronic inflammation may further exacerbate the already heightened CVD risk observed in people with HIV. Investigation of the cardiovascular complications of perinatal HIV infection has largely focused on youth and adolescents. Abnormalities in cardiac structure and function have been well documented and include systolic and diastolic dysfunction, left ventricular hypertrophy and dilatation, and myocardial fibrosis.[95-99] Studies of perinatally acquired HIV have also demonstrated elevated rates of surrogate markers of atherosclerosis (including carotid intima-media thickness, arterial stiffness, and endothelial dysfunction),[100,101] impaired glucose metabolism and insulin resistance,[102] lipodystrophy and metabolic syndrome,[103] and increased Pathobiological Determinants of Atherosclerosis in Youth (or PDAY) cardiovascular risk scores.[104,105] Adults with perinatally acquired HIV also appear to be at risk for cardiometabolic comorbidities, with a large North American study of young adults aged 18 to 30 years demonstrating a high incidence of DM, hypercholesterolemia, hypertriglyceridemia, hypertension, and chronic kidney disease.[106] Current gaps in knowledge regarding CVD risk among those who acquired HIV perinatally or during adolescence include (1) the clinical significance of cardiac structural and functional abnormalities and surrogate markers of atherosclerosis with respect to coronary plaque and cardiac endpoints; (2) whether the epidemiology and pathophysiology of CVD differ for people with similar durations of perinatally versus horizontally acquired HIV, including HIV acquired during adolescence; (3) whether the epidemiology and pathophysiology of CVD differ for people in low- and middle-income versus high-income countries; (4) the optimal approach to estimate ASCVD risk and frequency of monitoring in adults who acquired HIV perinatally or during adolescence; and (5) whether primary prevention approaches (e.g., statins) for adults with HIV aged 40 and older apply to younger adults who acquired HIV perinatally or during adolescence.

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Weight Gain in People With Treated HIV

Updated: September 25, 2025
Reviewed: September 25, 2025

Panel's Recommendations and Key Considerations
• All people with HIV should receive antiretroviral therapy (ART) to reduce morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI).** • Weight gain after ART initiation is common. ART initiation should not be delayed because of concerns for weight gain **(AIII),** and ART should not be interrupted or discontinued because of weight gain **(AIII).** • ART selection, whether for initiation or switch, should be based on optimization of virologic suppression. Specific antiretrovirals should not be selected to prevent or reduce weight gain **(AII),** as available evidence suggests this strategy is ineffective. • Providers should include weight monitoring in conjunction with counseling on strategies for weight control as part of comprehensive care for people with HIV.
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

Weight gain is an increasingly recognized and now expected consequence of antiretroviral therapy (ART) initiation in many people with HIV. Although the mechanisms of weight gain after ART initiation remain unclear, the pathogenesis is complex and multifactorial.[1,2]

Historically, weight gain following ART initiation was thought to be related to a "return to health" phenomenon, given that early in the HIV epidemic, many people suffered from AIDS-wasting syndrome before receiving lifesaving ART. Although "return to health" may explain some weight gain for people with advanced HIV, weight gain occurs regardless of the time between HIV acquisition and ART initiation, including among people who initiate ART shortly after HIV seroconversion.[3-5] Similarly, weight gain with ART initiation occurs with most modern regimens and regardless of baseline body mass index (BMI).[6-9]

People with HIV on ART may experience greater weight gain than the expected age-related changes in people without HIV.[10] The greatest weight gain often occurs within the first 2 years after ART initiation. Notably, pooled data from eight randomized controlled trials suggest that approximately 13% of people with HIV experience excessive (>10%) weight gain within the first year of ART initiation.[11] The average weight gain trajectory frequently slows after 2 years on ART.[10,11] Overall, studies differ on the amount of weight gain seen in people with HIV, depending on the ART regimen and study population.

Weight gain among people with HIV is further complicated by the obesity epidemic in the general population in the United States.[10,12] Importantly, some people with HIV experience a differential weight gain after ART initiation, with increased central fat and/or visceral fat gain, generally termed "lipohypertrophy."[2] Generalized weight gain and obesity can obscure the diagnosis of HIV-associated lipohypertrophy, which can carry additional cardiometabolic risk. Yet, no clear definition or consensus exists to distinguish HIV-associated lipohypertrophy from generalized weight gain following ART or from weight gain unrelated to HIV.

Although weight gain after ART initiation is common, the lack of a clear understanding of its pathogenesis has limited the development of HIV-specific prevention and/or treatment guidance. Thus, what follows is a synopsis of contributors to weight gain in people with HIV and general management considerations, based on available data.

Contributors to Weight Gain

Antiretroviral Therapy

Because weight gain is common with almost all ART regimens, antiretrovirals (ARVs) have been implicated as contributors to weight gain in people with HIV, although data on the mechanisms of ART-induced weight gain are limited. The differential effects observed between ART classes, as well as within-class variability, suggest the possibility of multiple mechanisms by which ARVs contribute to weight gain.

Contemporary Antiretroviral Drugs

Weight gain occurs with nearly all ART regimens, although some are associated with more weight gain than others. For example, the least weight gain occurs with some non-nucleotide reverse transcriptase inhibitor (NNRTI)–based and tenofovir disoproxil fumarate (TDF)–based regimens.[6-9] Weight gain is most pronounced with integrase strand transfer inhibitors (INSTIs), especially bictegravir and dolutegravir, and the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir alafenamide (TAF),[11,13] especially when compared to protease inhibitors (PIs) and older NRTIs.[6,11,13-19] The reasons for differential weight gain among ARVs are unknown. Importantly, differences in weight changes between ART regimens that are described in switch studies may be explained either by a weight-gain effect from exposure to a specific ARV (e.g., INSTI or TAF) and/or the removal of a weight-reduction effect from the ARV(s) that was discontinued (e.g., efavirenz or TDF). Some experts have suggested that medication side effects and/or unknown factors limit weight gain with certain older ARVs, when compared to the newer ARVs that have been linked to greater weight gain. Additional details and specific weight changes associated with individual ARVs can be found in the INSTI and NRTI sections of the guidelines.

Legacy Effects of Older Antiretroviral Drugs

The impact of prior ARV toxicity on an individual's current weight should also be considered. People with HIV who received thymidine analog NRTIs (e.g., zidovudine, stavudine) and older PIs (e.g., indinavir) were at risk for developing lipodystrophy. Lipodystrophy encompasses both lipohypertrophy (i.e., accumulation of visceral adipose tissue [VAT] and subcutaneous adipose tissue accumulation in the dorsocervical region, trunk, and/or breasts) and lipoatrophy (i.e., the loss of subcutaneous adipose tissue predominantly from the face, buttocks, and extremities).[2,20] Lipodystrophy can persist despite stopping the implicated ARV drugs. Particularly in individuals with lipoatrophy, subcutaneous adipose tissue fibrosis can persist and limit normal re-expansion of the fat depot when weight gain (from any cause) occurs, promoting VAT accumulation and its sequelae.[21] Thus, weight gain distribution and consideration of its effects on cardiometabolic risk may need to be contextualized by both prior and current ART exposure.

Individual Risk Factors and Population Differences

Although studies are limited, the following populations and clinical characteristics may contribute to greater ART-associated weight gain: female sex, older age, Black race/African descent, greater HIV disease severity (including lower CD4 T lymphocyte cell count and/or higher HIV-1 RNA),[11] and those who switched from a PI- or NNRTI-based ART regimen to an INSTI-based ART regimen while virologically suppressed.[6,11,22] Data on the influence of weight prior to ART initiation or switch are

conflicting, with some studies showing lower and others higher weight as a risk factor for subsequent ART-associated weight gain.[11,22]

Consequences of Weight Gain

Weight gain in people with HIV undoubtedly contributes to obesity-related comorbidities. In two Advancing Clinical Therapeutics Globally (ACTG) network protocols of longitudinal cohorts of people with HIV, individuals who experienced >10% weight gain within a year of ART initiation had an increased risk of type 2 diabetes mellitus (DM), metabolic syndrome, and cardiometabolic events 48 weeks after ART initiation.[23] Moreover, weight gain in people with HIV may confer a greater risk of cardiometabolic disease compared to people without HIV. The Veterans Aging Cohort Study found that each 5-pound weight gain was associated with a 14% greater risk of DM for people with HIV compared to 8% greater risk in people without HIV.[24] The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort observed an 18% to 20% increased relative risk of cardiovascular disease (CVD) per 1.0 kg/m^2 BMI increase among people with HIV who had a normal weight at ART initiation.[25] In comparison, a cohort of people without HIV from Finland demonstrated a 4% to 5% increase in CVD risk per 1.0 kg/m^2 BMI increase.[26] Thus, even small amounts of weight gain in people with HIV could potentially contribute to increased cardiometabolic risk, and any weight gain >10% from baseline weight has been strongly associated with incident DM, metabolic syndrome, and other cardiometabolic outcomes.[23]

Management of HIV-Associated Weight Gain

General Antiretroviral Therapy Considerations

Data on effective strategies to prevent or reverse ART-associated weight gain remain limited. Although weight gain among people with HIV likely increases risk for multiple cardiometabolic comorbidities and can negatively affect body image and psychosocial functioning, early and sustained ART treatment is critical to optimize short- and long-term clinical outcomes in people with HIV. ART initiation should not be delayed because of concerns for weight gain **(AIII),** and ART should not be interrupted or discontinued because of weight gain **(AIII).** ART selection should be based on optimization of virologic suppression. Specific ARVs should not be selected (for initiation or switch) to prevent or reduce weight gain **(AII),** as available evidence suggests that this strategy is ineffective. Specifically, greater average weight gains associated with INSTI- or TAF-based regimens should not influence decisions on regimen selection, especially in cases when these agents are likely to be the best option for effective virologic suppression, as the reasons for these differential effects on weight among specific ARVs are not clear.

Sustainable Lifestyle Modifications and Behavioral Weight Loss Programs

Lifestyle modification remains the starting point and gold standard weight management intervention. As in the general population, people with HIV should be educated on long-term healthy eating habits and encouraged to exercise regularly. Some individuals may benefit further from consultation with a licensed dietitian, nutritionist, and/or formal behavioral weight loss program, where available. Of note, few studies have evaluated behavioral weight loss programs specifically in people with HIV, although available data suggest they achieve outcomes similar to those seen in the general population.[27-29] Referral to an obesity medicine specialist and/or bariatric surgery center should be considered for select individuals.

Pharmacotherapy Targeting Adipose Tissue and/or Weight in People With HIV

Currently, there is not enough population-specific evidence for the Panel to recommend weight loss pharmacotherapy for people with HIV beyond what is recommended for the general population. Several therapeutic trials have been conducted targeting abnormal adipose tissue accumulation in people with HIV; some of the medications tested in these trials also cause weight loss, as discussed below.

Tesamorelin, a synthetic growth hormone–releasing hormone analog, is the only U.S. Food and Drug Administration–approved therapy to treat excessive abdominal fat in people with HIV. The efficacy and safety of tesamorelin were largely established by two large Phase 3 trials conducted in people with HIV with central obesity. Tesamorelin 2 mg given as a daily subcutaneous injection was associated with a 13.1% reduction in VAT from baseline over 26 weeks, representing a 15.4% relative reduction compared to placebo. Through 52 weeks, the reduction from baseline reached 17.5%, demonstrating that most VAT loss occurred during the first 6 months of treatment.[30] Although the participants enrolled in the initial trials were primarily treated with the older NNRTIs and PIs used at the time, another small randomized controlled trial demonstrated similar results among people with HIV taking INSTI-based regimens.[31] The use of tesamorelin, however, is limited by modest response rates (two-thirds of the participants with clinically significant VAT reduction), the need for weekly reconstitution, daily subcutaneous injections, and reversal of effects with drug discontinuation.

Glucagon-like peptide-1 (GLP-1) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (RAs) have gained considerable popularity in the general population due to the significant weight loss effects along with reduced risk for multiple CVD outcomes. However, few studies exist among people with HIV. The only randomized controlled trial to date in HIV was conducted in 108 participants with HIV-associated lipohypertrophy and overweight or obese BMI who received subcutaneous semaglutide 1.0 mg or placebo weekly over 24 weeks (plus an 8-week titration phase). People with DM were excluded from study entry. Semaglutide treatment resulted in an estimated weight loss of 10.4%, with significant reductions in total body fat and abdominal total and VAT.[32] In ACTG A5371, a 24-week, open-label, single-arm study of semaglutide 1.0 mg weekly for the treatment of metabolic dysfunction–associated steatotic liver disease in people with HIV who did not have DM, significant improvements in liver fat and other cardiometabolic parameters occurred that strongly correlated with weight loss (average of 8.1%).[33]

Although the few studies conducted in people with HIV showed an adverse event profile similar to the general population, the 1.0-mg dose used is lower than the maximum currently approved 2.0- and 2.4-mg doses for DM and obesity in the general population, respectively. Thus, the safety and side effect profile of GLP-1 and GLP-1/GIP RAs at higher doses or longer duration in people with HIV are currently unknown. Until more data become available, the Panel on Antiretroviral Guidelines for Adults and Adolescents advises prescribing GLP-1 and GLP-1/GIP RAs among people with HIV based on current general population indications and prescribing information.

Other weight loss drugs are available with and without a prescription in the United States and should similarly be used in accordance with general population recommendations. It is important to recognize the potential for known or possible drug–drug interactions with ARV drugs when considering the use of such therapeutic agents. For example, some case reports link orlistat, which promotes weight loss by reversibly inhibiting lipase and reducing dietary fat absorption, to loss of virologic suppression due to decreased ARV drug absorption.[34,35] In another example, the use of naltrexone-bupropion requires increased drug monitoring when coadministered with certain ARVs that may affect expected pharmacokinetic parameters.[36] Thus, it is critical to evaluate for any drug–drug interactions or possible adverse effects that may preferentially affect people with HIV on ARVs.

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CONSIDERATIONS FOR ANTIRETROVIRAL USE IN SPECIAL POPULATIONS

Adolescents and Young Adults With HIV

Updated: September 24, 2026
Reviewed: September 24, 2026

Key Considerations and Recommendations
• AYA with HIV largely belong to two distinct groups: (1) those who acquired HIV perinatally (intrauterine, intrapartum, or during breastfeeding), and (2) those who acquired HIV non-perinatally. • All AYA with HIV should initiate ART as soon as possible and stay on it indefinitely to maximize viral suppression, reduce morbidity and mortality, and prevent secondary HIV transmission **(AI).** • It is critically important to assess behavioral and psychosocial context, as these impact adherence to ART. Efforts should be made to provide youth-friendly, strengths-based support and infrastructure to reduce barriers to adherence and maximize success in achieving sustained viral suppression**.** • 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 population and the challenges that frequently accompany their transition. 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**.**
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*

Key: ART = antiretroviral therapy; AYA = adolescents and young adults

Introduction

Adolescents (13–19 years old) and young adults (20–24 years old) (AYA) with HIV are largely divided into two distinct groups—those who acquired HIV perinatally (intrauterine, intrapartum, or during breastfeeding) and those who acquired HIV non-perinatally. In the United States, most pregnant women with HIV receive effective antiretroviral therapy (ART) during pregnancy and postpartum, which has significantly reduced the prevalence of AYA who acquired HIV perinatally. As a result, the majority of AYA with HIV have non–perinatally acquired infection. These individuals have lower rates of testing and diagnosis and linkage to care than adults with HIV.[1,2] Importantly, unique developmental, psychosocial, behavioral, and infrastructural factors affect this population. Without having their specific challenges and needs addressed, some AYA with HIV are at risk for poorer HIV-related outcomes, including persistent viremia, drug resistance, morbidity, mortality, and secondary transmission. This section of the Guidelines focuses on issues unique to AYA with HIV and provides guidance on ways to optimize care and achieve the best clinical outcomes.

Epidemiology

The Centers for Disease Control and Prevention estimates that 19% of the individuals newly diagnosed with HIV in the United States between 2020 and 2024 are AYA.[3] The majority of new diagnoses in this age group are among Black/African American and Hispanic/Latino males who identify as men who have sex with men (MSM). In 2024, 48% of the new infections in this age group

were among young Black and African American AYA, and 35% were among Hispanic and Latino AYA; at least 81% were attributed to male-to-male sexual contact and 14% to heterosexual contact. Compared with 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 greater among youth aged 13 to 24 years than among those older than 24. Among the 28,000 AYA with HIV in the United States, approximately 23,000 are being followed at pediatric and adult clinics.[3,4]

Heterogeneity of Adolescents and Young Adults With HIV

AYA with HIV represent a diverse population in terms of sociodemographics, 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.

Adolescents and Young Adults With Perinatally Acquired HIV

AYA who acquired HIV perinatally (intrauterine, intrapartum, or during breastfeeding) are more likely to be treatment-experienced and may have antiretroviral (ARV) drug resistance that affects their options for ART regimens.[5] This may be even more relevant for AYA with HIV who emigrated from countries where routine viral load and genotypic resistance testing are not readily available; thus, 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 than those who acquired HIV after the first decade of life.[6-9]

Adolescents and Young Adults With Non–Perinatally Acquired HIV

The vast majority of AYA with diagnosed HIV in the United States fall into the category of non–perinatally acquired HIV. Individuals in this group are a more heterogeneous group of mostly young men (especially MSM) and other people who acquired HIV primarily through sexual contact; very few (<5%) AYA with diagnosed HIV report acquisition through injection drug use.[3] The intersection of AYA with other key risk populations (e.g., adult MSM, people who use drugs, sexual networks with high HIV prevalence) magnifies the risk of poor clinical outcomes in this younger population.[10-12] One study found that a higher percentage of individuals in this group reported extensive negative life experiences (14–21 events) than those with perinatally acquired HIV (39% vs. 16%, $P < 0.012$).[13]

Less commonly, HIV acquisition may occur earlier in childhood via premastication of food,[14] exposure to contaminated blood products or nonsterile medical procedures, or sexual contact (e.g., sexual abuse).[15] AYA who acquire HIV through these pathways may share some clinical and psychosocial experiences with those who acquired HIV perinatally, including early life diagnosis, prolonged engagement with health care systems, and developmental or mental health challenges.

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 with adults aged 25 years and older, AYA with HIV have been shown to have poorer outcomes on each step of the HIV care continuum.[16,17] Most notably, <60% of AYA with HIV have been diagnosed, and <40% are virally suppressed; these numbers are significantly worse than

documented in older adults with HIV.[18] In one study of MSM of all ages, the percentage of those linked to HIV care within 1 month of diagnosis was lowest among AYA with HIV aged 13 to 19 years (69%) and 20 to 24 years (70%).[19] This group also had the lowest rates of retention in care and viral suppression. Older young adults (aged 25–34 years), who currently have the highest incidence of HIV infection among all age groups, have similar challenges, with nearly 30% unaware of their infection status.[18] They, too, require focused attention.

Some improvements, albeit modest, have been made in recent years. National HIV Surveillance System data have shown increases in knowledge of status (from 40% to 56%), linkage to care within 1 month of diagnosis (from 75% to 82%), and viral suppression (from 57% to 69% among those diagnosed) between 2017 and 2022/2023. However, there remains significant room to accelerate progress toward improved outcomes for AYA.[20]

Key features that are specific to AYA with HIV should be considered carefully because they can affect HIV treatment and may alter clinical decision-making. These features are discussed below.

Developmental Changes and Engagement in Care

During adolescence and young adulthood, AYA with HIV experience socioemotional, cognitive, and developmental changes that may impact their engagement in medical care. Developmental maturity in AYA with HIV generally can be grouped into several, often overlapping, areas, including physical, cognitive, communication/language, social, emotional, and sexual maturity. 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 AYA with HIV. Additional psychosocial factors detailed in Unique Psychosocial Factors are also common in this population and can influence development and HIV treatment outcomes.

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 decision-making capacity is often driven by concrete thinking processes and limited frontal lobe maturation, which can result in a focus on immediate rather than long-term gratification. AYA experience a strong desire for independence, preoccupation with self-image, and a significant focus on the opinions of their peers; all of which have the potential to affect medication adherence and long-term clinical outcomes.[9,21-23] Likewise, some AYA with HIV are at risk for neurocognitive impairment and mental health comorbidities,[24-27] including psychiatric, behavioral, and substance use disorders, which can further affect cognitive development and compromise effective HIV treatment.

Physical Development

The rapid physiologic changes that occur in adolescence (e.g., puberty, rapid growth) may result in altered ARV pharmacokinetics (PK), underscoring the importance of adolescent-specific studies.[9] AYA with HIV, particularly those who acquired HIV early in life and/or while sexually immature, also are at risk for impaired physical development, especially delayed sexual maturation and impaired 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.[28] Both delayed maturation and short stature may increase anxiety, depression, and stigma, which may, in turn, affect treatment adherence.[29] AYA with non–perinatally acquired HIV may also 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 age-matched controls without HIV.[30]

Thus, developmental maturity should be considered in AYA with HIV, because associated clinical implications may alter HIV treatment decisions, including ARV selection and dosing.

Unique Psychosocial Factors

Several psychosocial, behavioral, and environmental risk factors affect many AYA with HIV and can undermine successful HIV treatment disproportionately in this population. Lack of access to services (e.g., for mental health or substance use disorders) remains a major barrier to successfully addressing these factors. Common key risk factors are summarized below.

Behavioral and Mental Health

The percentage of AYA with HIV with behavioral and mental health conditions is 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. Adolescents with perinatally acquired HIV have especially high rates of mental health conditions, nearly 70% meet criteria for a psychiatric condition at some point in their lives.[26,31-34] Similarly, among AYA with HIV presenting for care at treatment sites in the Adolescent Trials Network, depression and anxiety were identified by symptom inventory 43% and 31% of the time, respectively.[35] These conditions can create a syndemic that further contributes to poor adherence, virological failure, and HIV-associated neuroinflammation, all of which can exacerbate mental health disorders.[36]

Substance Use

Substance use is prevalent among AYA with HIV. Among more than 2,000 AYA with HIV (72% non–perinatally acquired) 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.[37,38] Young MSM had higher odds of each substance use behavior. Studies have suggested that substance use contributes to HIV risk through medication nonadherence, sexual violence, internalizing of mental health, and condomless anal sex, with some samples reporting prevalence of polysubstance use as high as 86%.[39-41] Suboptimal ART was associated with increased risk of substance use behaviors,[37] underscoring the need to screen for and address substance use to improve treatment outcomes.

Unstable Housing

Data from the early 2000s found substantially higher rates of HIV among unhoused youth than among the general population.[42] In a more recent nationally representative survey of high school students, respondents from multiple racial and ethnic groups (American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Black) and sexually minoritized youth experienced disproportionate rates of housing instability; youth with unstable housing also reported higher rates of substance use and suicidal ideation than their housed peers.[43] National surveillance data show that unstable housing and homelessness are more common among young adults with HIV aged 18–24 years (37%) than among those aged 25 years and older (18%).[44] AYA with HIV and unstable housing have greater difficulties securing and sustaining resources and engaging in and being retained in care and treatment, and they are at risk for sexual coercion and transactional or survival sex (e.g., sex for money or a place to stay).[45,46]

Trauma

AYA with HIV may disproportionately experience trauma. According to 2023 Youth Risk Behavior Survey data among the general population, 76.1% of high school students reported one or more

adverse childhood experiences (ACEs), and 18.5% reported four or more.[47] The most common ACEs reported in the sample were emotional abuse (61.5%), physical abuse (31.8%), and household poor mental health (28.4%). Populations of youth that are disproportionately impacted by HIV, including multiracial youth and youth who identified as gay, lesbian, or bisexual, or who described their sexual identity in some other way, experienced the highest number of ACEs. The proportion of ACEs in AYA with HIV is not well studied; however, large adult data analyses suggest that as high as 82% of people with HIV experience one or more ACE,[48] while smaller AYA-focused data have demonstrated this proportion is closer to one-third.[49] Evaluating for the presence of ACEs is important, given data in Black and Latine AYA with HIV found that a history of ACEs was associated with lower odds of engagement in HIV care.[50]

There is a lack of guidance specific to the frequency of and tool used to assess ACEs in clinical practice. Current research suggests that screening for ACEs be part of a trauma-informed approach that has the potential to identify previous or current experiences that could contribute to poor health outcomes (e.g., violence, housing instability, food insecurity).[51] More research is needed to better understand the best screening approaches in AYA with HIV; the potential benefits, challenges, and harms of routinely screening; and the best approach for addressing ACEs in clinical settings and determining how they may impact ART outcomes.

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.[52]

Optimizing Treatment Effectiveness and Supporting Adherence in Adolescents and Young Adults With HIV

Given the unique physiological, developmental, and psychosocial characteristics discussed above, AYA with HIV require comprehensive systems of care with providers with adolescent-specific expertise and tailored treatment to serve all their specific medical and psychosocial needs. To maximize their chances of success, it is 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 Adherence to Antiretroviral Therapy in Children and Adolescents With HIV in the Pediatric ARV Guidelines for additional approaches. Targeted interventions to improve treatment effectiveness and adherence related to a few key psychosocial factors among AYA with HIV also are highlighted in the sections below.

Neurocognitive Considerations

Neurocognitive disorders and limitations are pervasive among AYA with HIV and may be due to HIV neuropathogenesis that occurs during early infection, uncontrolled viremia, and/or virus in the central nervous system, even during aviremic states.[7,53,54] Additional factors, such as intrauterine exposures, trauma, and psychosocial stressors, may exacerbate the risk of developing neurocognitive dysfunction. AYA with perinatally acquired HIV have an increased risk of neurocognitive challenges, including cognitive impairment. A recent meta-analysis highlighted limitations in processing speed, working memory, and, to a lesser degree, executive function compared with matched controls without HIV.[55] In a prospective study, an estimated 65% of young

adults aged 18 to 24 years with non–perinatally acquired HIV had evidence of HIV-associated neurocognitive disorders, and impairments in executive and motor function as well as verbal memory. Notably, histories of special education (22%) and needing to repeat a grade (22%) preceded the HIV diagnosis, suggesting some premorbid limitations.[54,56] Another study demonstrated that young adults aged 18 to 24 years with HIV had poorer executive function than seronegative controls.[57] Data are limited but suggest that neurologic impairment is at least as prevalent as in older adults despite lower viremia, higher CD4 count, and shorter durations of infection in AYA.[54] Given that the neurocognitive limitations may be subtle and are often underrecognized, attaining formal neurocognitive assessments can be critical to identifying potential challenges and providing access to resources where available. Using clear, simple, concrete language with accompanying visual aids and other modalities (e.g., videos, graphics), read-back/teach-back, and other strategies may be critically important to ensuring an understanding of instructions related to ART and other aspects related to HIV treatment and care. Strategies for understanding and mitigating the development of neurocognitive disorders remain active areas in need of research.

Mental Health Care

AYA with HIV are at increased risk for mental health disorders, including depression, anxiety, and post-traumatic stress disorder.[58] 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.[59,60] These strategies include improving provider education, integrating trauma-informed care practices, increasing access to mental health professionals through co-located 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.[61,62] Screening for mental health disorders should be done routinely and systematically using tools validated in adolescents (e.g., Patient Health Questionnaire [PHQ-2[63] and PHQ-9[64]], Generalized Anxiety Disorder [GAD-7][65,66]). A recent review of evidence-based guidelines highlighted different models and the need for further research on strategies that can effectively address mental health in AYA with HIV.[59,67] Further guidance for providing appropriate mental health care for AYA with HIV can be found in the Pediatric ARV Guidelines.

Substance Use Disorders

Providers should routinely assess and recommend treatment for substance use disorders, with consideration of emerging substance use trends, such as the use of electronic vapor products and marijuana,[68] which can impact the HIV care continuum for AYA with HIV.[69] The American Academy of Pediatrics recommends the use of a validated tool, such as the S2BI (Screening to Brief Intervention) or BSTAD (Brief Screener for Tobacco, Alcohol, and other Drugs), to screen first, followed by a risk-stratified assessment tool like CRAFFT, a clinical questionnaire used to identify problems associated with substance use.[70] Further guidance for providing appropriate substance use screening and treatment for AYA with HIV can be found in the Pediatric ARV Guidelines and in the Substance Use Disorders and HIV section.

Psychosocial and Environmental Stressors

Many AYA with HIV have significant numbers of social determinants of health (SDOH), such as poverty, limited education, food insecurity, intimate partner violence, and insurance gaps. Compared with adults with similar numbers of SDOH indicators, AYA with HIV have worse HIV outcomes.[71] 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 ARV drugs 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 high barrier to resistance alongside an individualized assessment of existing and potential adherence barriers and available youth-friendly support strategies to facilitate adherence.[72] Additional considerations and strategies that may affect adherence among AYA with HIV are highlighted below in Table 11.

Table 11. Strategies to Improve Antiretroviral Therapy Adherence

Category	Strategies to Improve ART Adherence
Regimen selection	• Simple ART regimens (e.g., fixed-dose, once daily combinations) with high barriers to resistance are preferable, if possible. • Long-acting injectables may also be considered, including for youth with adherence challenges due to social environment (e.g., unstable housing, coexisting substance use). • Minimal side effects • Small pill size
Treatment plan	• Develop the plan in partnership with AYA with HIV, considering daily schedule; disclosure; tolerance of pill number, size, and frequency; issues affecting absorption; dietary considerations; and potential adverse effects and interactions with other medications. • Design youth-friendly reminder systems (e.g., apps, cell phone/text reminders, pill boxes) for adherence support.
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.

Key: ART = antiretroviral therapy; AYA = adolescents and young adults

Antiretroviral Therapy Regimens for Adolescents and Young Adults With HIV Without Drug Resistance

The recommendations for initial ARV regimens for AYA are the same as for the general population (see What to Start). Clinical trials have demonstrated the superiority of dolutegravir (DTG) over boosted protease inhibitor–based regimens. Bictegravir (BIC) coformulated with tenofovir alafenamide (TAF) and emtricitabine (FTC) also has a low risk of treatment-emergent resistance and is available as a single-tablet regimen with a small pill size and no food requirements. Adolescents

aged ≥12 years and weighing ≥35 kg can be treated with an adult fixed-dose combination of BIC/FTC/TAF given favorable PK and viral suppression results in a stable adolescent switch study.[73]

Several two-drug ARV regimens are effective as initial therapy or as a switch therapy in people who achieved viral control and have no resistance to the ARV drugs in the combination; some examples include oral regimens of DTG plus lamivudine, DTG plus rilpivirine (RPV), doravirine plus islatravir, and the long-acting (LA) injectable combination of cabotegravir (CAB) plus RPV (or LA CAB/RPV). However, none of these two-drug regimens are effective as treatment for hepatitis B virus (HBV), and they are not recommended for AYA with HBV/HIV coinfection, because using these regimens in individuals with concomitant HBV infection risks HBV flaring (see HBV/HIV Coinfection for more details).[74]

LA CAB/RPV, given intramuscularly on a monthly or every-two-month schedule, is U.S. Food and Drug Administration–approved in the United States for individuals with HIV who are engaged in care and virally suppressed on oral therapy. These agents have been studied in adolescents with HIV aged 12 to 17 years, weighing ≥35 kg,[75-77] and virally suppressed on oral ART without relevant ARV resistance.[76] Among adolescents who switched from oral ART, LA CAB/RPV demonstrated sustained viral suppression, a favorable safety profile, and high acceptability and tolerability. Some AYA with HIV who have a history of nonadherence may have high interest in LA regimens.[78,79] Case series of viral suppression with the use of LA CAB/RPV[80] in AYA with HIV with a history of poor adherence are encouraging.[81,82] Studies to evaluate these modalities among nonadherent individuals, including AYA with HIV, are needed,[83] and those including AYA with HIV are underway (see NCT06694805).

Antiretroviral Therapy–Experienced Adolescents and Young Adults With HIV and 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 mirror those of older ART-experienced adults, such as extensive drug resistance, complex regimens, and adverse drug effects. It is critically important to assemble a comprehensive ARV history and cumulative HIV genotype/phenotype test results to fully appreciate the extent of archived resistance mutations. 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.[84] Acquired treatment-emergent integrase strand transfer inhibitor resistance may occur.[85] Further, the advent of newer agents with novel mechanisms of action (e.g., fostemsavir, ibalizumab, lenacapavir) presents the opportunity to design suppressive regimens for AYA with drug resistance (see Virologic Failure), including those in need of fully injectable regimens.

Antiretroviral Therapy Considerations in Sexually Immature Adolescents and Young Adults With HIV

The physiological changes (e.g., puberty, rapid growth) that occur in adolescence may result in altered PK. 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 ARV 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 rapidly growing adolescents. 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 tenofovir disoproxil fumarate, because of a greater bone loss with the latter ARV drug.

For a more detailed discussion on ART therapy in AYA with HIV, please see the What to Start section and the Pediatric ARV Guidelines. For additional information on treatment adherence in AYA with HIV, please see Adherence to the Continuum of Care, Adherence to Antiretroviral Therapy in Children and Adolescents With HIV, and Modifying Antiretroviral Regimens in Children With Sustained Virologic Suppression on Antiretroviral Therapy.

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, type 2 diabetes mellitus (DM), metabolic syndrome, osteoporosis, and neurocognitive impairment. When HIV is acquired at birth or early in life, an individual can live for many decades. However, changes indicative of premature aging and earlier onset of multiple comorbidities have been documented.[86] Data from NA-ACCORD found elevated rates of DM (19%), hypercholesterolemia (40%), chronic kidney disease (25%), and other cardiometabolic conditions among young adults aged 18 to 30 years with perinatally acquired HIV.[87] 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, steatohepatitis, 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 the 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 teen-centered and multidisciplinary, with primary care highly integrated into HIV care.[88] Often, the setting is discrete, 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 often “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; availability of telemedicine when appropriate; 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 AYA to separate subspecialty care settings, such as gynecology. Furthermore, adult clinic settings tend to be larger and can easily intimidate younger, less motivated AYA.[89]

When transitioning the care of an AYA with HIV, one 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 show variable rates of successful transition to adult care ranging between 50% and 85%.[90-93]

It is important to recognize that the transition for AYA with HIV acquired perinatally versus those who acquired HIV non-perinatally may pose distinct challenges. AYA with HIV who acquired HIV perinatally—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 non-perinatally, 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; however, engagement levels vary, as some may be highly engaged with the pediatric program where they may have received care since being diagnosed. Either group may perceive the transition as a major loss or disruption in their social support. Factors to date that have been associated with successful transition for those with HIV acquired perinatally include high self-management and perceived emotional and social support.[94,95]

To maximize the likelihood of a successful transition, interventions to facilitate transition are best implemented early on.[89,92,93,95] Strategies and approaches for both the adult and pediatric or adolescent programs are discussed in Table 12 below.

Table 12. Approaches to Optimize Transition to Adult Care for Adolescents and Young Adults With HIV

Pediatric/Adolescent	Adult
Personnel	
• Engage a team knowledgeable about medical and psychosocial issues of AYA with HIV, including the challenges of transitioning youth to adult care settings. • Utilize providers with training in medical care across the lifespan, if available, and discuss distinct models of care (i.e., HIV providers as primary care physicians vs. as consultants) with AYA. • Assign a transition point person and have their contact information readily available. • Educate clinic personnel about transitioning AYA with HIV and their needs. • Encourage a member of the pediatric care team to attend the first appointment with the adult provider if feasible.	• Engage an adult care team knowledgeable about medical and psychosocial issues of AYA with HIV, including the challenges of transitioning youth to adult care settings. • Utilize providers with training in medical care across the lifespan and ensure adequate training of adult providers to care for AYA with HIV. • Assign a transition point person and have their contact information readily available. • Identify and engage outreach specialists, navigators, social workers, case managers, and providers with a youth-friendly approach. • Educate clinic personnel about intersection and structural stigmas that many AYA with HIV experience. • Train personnel in cultural competence to address intersectional and structural stigmas that AYA with HIV experience.

Table 12. Approaches to Optimize Care Transition for AYA With HIV

Pediatric/Adolescent	Adult
	• Encourage a member of the pediatric care team to attend the first appointment with the adult provider if feasible.
Education and Preparation of AYA With HIV	
• Enhance AYA with HIV health literacy, including understanding of HIV and their medical history. • Address resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles. • Help AYA develop life skills, including, but not limited to, counseling on appropriate use of a primary care provider and how to manage appointments; prompt symptom recognition and reporting; and self-efficacy in requesting prescriptions, arranging for transportation to appointments, and managing insurance and assistance benefits.	• If possible, meet AYA with HIV before transition, if possible. Clearly outline policies and expectations before and during the first visit, if possible. • Have an orientation plan to acquaint newly transitioned AYA with HIV to the clinic environment and adult clinical care program, including workflows that may be new to them (e.g., using an electronic portal to schedule appointments), and provide concrete examples of when to use different communication modalities (e.g., messaging, leaving a voicemail, paging). • Implement interventions that may improve outcomes, such as patient navigators, peer support groups, mental health assessment, and inclusion of guardians where available. • Address health literacy and ensure AYA with HIV understand HIV and goals of care. • Continue to work with AYA with HIV toward developing life skills, etc.
Strategies and Approaches	
• Develop a formal, 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, medical history handoff that includes prior regimens, outcomes (e.g., adherence, virologic failure and resistance), and primary data (e.g., dated genotypic resistance testing results) whenever possible.	• Develop a 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 a nuanced understanding of 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 if feasible), particularly when first transitioning. • Encourage physical spaces, structures, and pins that are supportive of AYA with HIV and their identities (e.g., youth-friendly art, pride flag, expedited rooming, separate waiting areas when space allows). • Incorporate other aspects of care beyond HIV management, if possible (e.g., family planning, sexually transmitted infection testing and treatment, mental health, substance use).

Table 12. Approaches to Optimize Care Transition for AYA With HIV

Pediatric/Adolescent	Adult
	• Close the loop with the pediatric/adolescent providers and encourage them to reach out if the AYA continues to contact their former clinic.
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 digital 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).	

Key: AYA = adolescents and young adults; HIPAA = Health Insurance Portability and Accountability Act

Discussions regarding transition should begin early and precede the actual transition process. Attention to the key interventions noted above will be likely to improve adherence to appointments and avoid the potential for youth to disengage from care during this period. For a more detailed discussion on specific topics related to transitioning care for AYA, see Transitioning to Adult HIV Care. Please also refer to the Pediatric ARV Guidelines.

Table 13. Adolescents and Young Adults With HIV Antiretroviral 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, pill boxes, support buddies/peers/groups)	• 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 high interest in long-acting alternatives for ART delivery. • May obviate disclosure concerns • Promising tool to facilitate adherence for AYA with HIV
	Directly observed therapy (in person or virtual) may be considered	• May provide support and oversight, particularly for AYA with barriers to independently taking ART.
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).
Side effects/fear of side effects	ARV regimens that minimize side effects Early and expeditious prevention, recognition, and management of side effects, with transparency about potential 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 and motivational enhancement therapy	• Motivational interviewing and motivational enhancement therapy acknowledge AYA with HIV's autonomy and potential ambivalence about treatment adherence. • Motivational interviewing and motivational enhancement therapy have shown promise for improving adherence to chronic disease treatment, including HIV.

Table 13. Adolescents and Young Adults With HIV Antiretroviral Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
	Positive affirmation messages (e.g., text, app, trusted messengers)	• Electronically delivered positive affirmation messages can improve self-esteem and ARV adherence among AYA with HIV. • Some advocacy groups provide other resources with positive affirmations that can improve self-esteem and ARV adherence.
Non-disclosure	Early disclosure and assistance with disclosure	• Early (by age 10–12 years) disclosure of HIV status for those with perinatally acquired HIV enhances adherence and self-esteem and limits stigma. • Assistance with disclosure to partners or peers may enhance outcomes, including self-esteem, self-acceptance, and mood.
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 or receiving LA CAB/RPV injections, 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.
Mistrust of providers and the medical establishment	Empathetic and patient-centered communication	• Communication exploring the needs of AYA with HIV can build trust, including exploring needs not directly related to HIV treatment (e.g., school, employment, relationships).
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.
Social isolation and lack of familial and social support	Family and peer support groups	• Family members and peers are a defense against stigma and social isolation, a source of emotional support, and partners in medication management.
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. • To reduce stigma and improve ARV adherence, providers should not conceptualize AYA with HIV as “high risk.”
Provider implicit biases regarding AYA with HIV	Implicit bias training	• Consciously changing biased associations and repeated bias self-regulation training can reduce providers’ implicit biases.

Table 13. Adolescents and Young Adults With HIV Antiretroviral 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 or adaptation of youth-friendly services	• Clinic days or hours dedicated to AYA with HIV patients better address unique adherence needs; youth-friendly services include the following: o Flexible hours, easy scheduling, telephone/telehealth appointments o Providers trained in working with AYA with HIV o Youth-friendly waiting rooms and physical spaces o Supplemental services that comprehensively address psychosocial and health needs of AYA with HIV o 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 using strategies such as— o Offering evening hours o Staff training on service delivery to AYA with HIV o 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: o Primary care and sexual and reproductive health services o Behavioral health services o Psychosocial support services (e.g., school support, transportation, support groups, housing and food assistance)

Table 13. Adolescents and Young Adults With HIV Antiretroviral Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
	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. • Emphasize strengths-based supports

Key: ART = antiretroviral treatment; ARV = antiretroviral; AYA = adolescent and young adult; LA CAB/RPV = long-acting cabotegravir plus rilpivirine; U=U = undetectable equals untransmittable

Knowledge Gaps

More research is needed related to the following:

- Safety and efficacy of LA injectable ART for AYA patients with viremia
- Best strategies for optimizing retention in care, the transition from pediatric-focused to adult-focused care settings, and clinical and virologic outcomes for AYA
- Metabolic complications associated with HIV and long-term use of ART in AYA with HIV and the effectiveness of preventive strategies (including cardiometabolic and bone health)
- The utility, affordability, scale-up, and cost-effectiveness of strategies for improving outcomes for AYA with HIV (e.g., retention in care, adherence to ART, earlier screening for metabolic complications in AYA)
- Understanding and evaluation of strategies for identifying and mitigating ACEs and the development of neurocognitive disorders in AYA with HIV
- Identifying effective interventions to address mental health and substance use disorders among AYA with HIV

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Early (Acute and Recent) HIV Infection

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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).** o Standard genotypic drug-resistance testing should be performed for mutations in the reverse transcriptase and protease genes **(AIII)** for all people with early HIV. o 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 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. o 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]) o 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 women 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

Four antiretroviral (ARV) options—oral emtricitabine (FTC) with either tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), intramuscular long-acting cabotegravir (CAB-LA), or subcutaneous lenacapavir—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 women 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 women 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 women 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 women of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII).**
- Pregnant women with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV **(AI).**

Table 14. Identifying, Diagnosing, and Treating Acute and Recent HIV Infection

- 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.
- 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

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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 now commercially available for clinical care.[10,11] 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[12]; 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.[13,14]

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.[15] HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs)[16]; 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[17,18] or regimens that contain an NNRTI plus two NRTIs.[19,20] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[21,22]

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*.[23-28] INSTI-based regimens have shown favorable treatment responses in observational studies.[29-31] 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.[32-34]

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.[13,14,22,35] Darunavir (DRV), lopinavir (LPV), and saquinavir are more active against HIV-2 than other approved PIs.[36-38] 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.[12,17,18,39,40]

Other Antiretroviral Drugs

Among the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.[41] The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates[42]; 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.[43] The post-attachment inhibitor ibalizumab (IBA) has potent *in vitro* activity against HIV-2 isolates.[44] Limited data suggest HIV-2 is intrinsically resistant to the attachment inhibitor fostemsavir (FTR).[45,46]

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.[47,48]

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection[49-52]; 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).**

Women with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as women 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.[53-55]

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.[38,56,57] Currently, transmitted drug resistance appears to be rare among people with HIV-2.[58,59] 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.[60-63] 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).[64] 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

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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). In addition, ARV regimen selection may be influenced by potential interactions between ARV medications and drugs used concomitantly to manage comorbidities (see the Liverpool HIV Drug Interaction Checker). 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 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 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 the Liverpool HIV Drug Interaction Checker). 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 or for other medical indications. 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, sex, 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 women with HIV are experiencing menopause. Although menopause may occur earlier in women with HIV than in 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 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.[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

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Key Considerations and Recommendations
• 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, cannabis/cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. • Health care providers should be nonjudgmental when addressing substance use with people who have 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) as part of comprehensive HIV care in clinical settings (see Table 15) **(AI).** • ART is recommended for all people with HIV **(AI).** Ongoing substance use is **not a contraindication** to 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, neurocognitive impairment, overdose). • Selection of ARV regimens for individuals with SUDs 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 effects of ART or substance use**.** • Once-daily ARV regimens (ideally as a single-tablet regimen) with high barriers to resistance, low hepatotoxicity, and low potential for drug–drug interactions are preferred for people with SUDs **(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*

Key: ART = antiretroviral therapy; ARV = antiretroviral; SUD = substance use disorder

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), adhering to ART, or remaining engaged in care. 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, neurocognitive impairment, 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 (4,296 deaths in 2024).[2] Given the expanding overdose epidemic and the impacts of both substance use and substance use disorders (SUDs) on optimal engagement in the HIV care continuum, health care providers need a basic understanding of how to screen for and treat SUDs in people with HIV in clinical settings.[3] As SUDs are prevalent among people with HIV and contribute to poor health

outcomes, screening for SUDs should be a routine part of clinical care **(AII).** Additionally, people with HIV and SUDs should be screened for mental health disorders **(AII).**

Substance use exists on a continuum, from episodic use to 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,[5] including among adolescents and young adults with HIV (see Adolescents and Young Adults With HIV). This section focuses on the most commonly used substances among people with HIV (listed in alphabetical order): alcohol, benzodiazepines, cannabis/cannabinoids, club drugs,[6] opioids, stimulants (cocaine and methamphetamines), and tobacco. Additionally, two common opioid adulterants (i.e., xylazine and medetomidine) with potential health consequences are 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, whereby drugs are intentionally used to enhance sexual activity (i.e., chemsex and sexualized drug use).[7] 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).[8] 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.[9] 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.[10] 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.[11] 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.[12,13]

Substance Use and Unstable Housing

People with HIV who inject drugs are more likely to be unhoused compared to those who do not inject drugs.[14] Houselessness among people who inject drugs is associated with an increased risk of HIV acquisition.[15]

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, adjusted for multiple intersecting risks—including unhealthy alcohol use, other substance use, incarceration, unemployment, education, age, sex, and race/ethnicity—houselessness was associated with a 41% to 54% decrease in the odds of being on ART, adhering to ART, and achieving viral suppression.[16] Among 6,873 people with HIV enrolled in the CFAR Network of Integrated Clinical Systems (CNICS), a 10-site clinical cohort of people with HIV engaged in care, 9.6% reported housing instability, including 4.6% with unstable housing, 3.3% homelessness, and 1.7% uncertainty about housing stability.[17] In the primary adjusted analysis, houselessness was associated with an 18% lower prevalence of viral suppression (95% confidence interval [CI], 0.77–0.89), and unstable housing was associated with a 6% lower prevalence of HIV viral suppression (95% CI, 0.90–0.98) than with stable housing. In a secondary analysis, houselessness was associated with a 21% lower prevalence of viral suppression among people reporting substance use (95% CI, 0.70–0.90). Interventions supporting housing among people with HIV and SUD can result in improved HIV treatment outcomes (see Adherence to the Continuum of Care). 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% CI, 1.1–4.0).[18,19] 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.[20] 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 any drugs (including benzodiazepines, cannabis/cannabinoids, club drugs, opioids, or stimulants) 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).[21] For individuals with liver disease, including active hepatitis B virus (HBV) and/or HCV infection or with metabolic dysfunction–associated steatotic liver disease, any alcohol use is considered unhealthy.

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 at-risk substance use and guide decisions on appropriate treatment interventions. Currently, insufficient data are available 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.[22,23] 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, American Medical Association, American Society of Addiction Medicine (ASAM), International Society of Addiction Journal Editors, and others have recommended the adoption of clinical, nonstigmatizing language for substance use, as described by the National Institute on Drug Abuse.

Co-occurring Mental Health Disorders

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.[8,24] 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 substance use without providing treatment for underlying mental health conditions has very limited efficacy.[25]

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 use of needles or 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 sterile drug preparation and injection supplies to reduce transmission of HIV, HBV, 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,[26] including those for treating SUDs.[27] For people with HIV, SSPs can be adapted to provide or link to rapid initiation[28,29] and maintenance of effective ART.[29]

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, HBV, or HCV), potential drug–drug interactions, and possible adverse events from ART or substance use. 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. Once-daily ART regimens (ideally as a single-tablet regimen)[30] with high barriers to resistance, low hepatotoxicity, and low potential for drug–drug interactions are preferred for people with SUDs **(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,[31,32] 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 engagement in HIV care and who are virally suppressed on oral therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral 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 viral suppression on oral therapy prior to starting LA ART. The LATITUDE study was an open-label randomized trial that compared switching ART to monthly LA CAB/RPV injections versus maintaining oral ART among people with viral suppression who had experienced adherence challenges. Participants who received LA CAB/RPV had lower rates of regimen failure, defined as two consecutive HIV viral load measurements >200 copies/mL, than those who continued oral ART (22.8% vs. 41.2%, respectively; $P = 0.002$). At baseline, 32% of participants reported hazardous alcohol use. During the study, 46% had at least two drugs identified through a urine drug screen. All participants in the LATITUDE study received adherence support throughout the study.[33] 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.[34]

The following factors should be considered when contemplating the use of LA CAB/RPV in people with HIV and SUDs:

- Prior to initiation of LA CAB/RPV, providers should review any prior antiretroviral (ARV) history and available resistance-testing results, with special attention to prior use of integrase strand transfer inhibitors (including prior use of LA CAB for pre-exposure prophylaxis) and/or non-nucleoside reverse transcriptase inhibitors, as well as virologic responses during treatment (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- For people with viremia, genotypic resistance tests should be obtained and results reviewed before switching to LA CAB/RPV.
- 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,[35] 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.[36]
- 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 succeed 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 some people with SUDs, clinical care teams should be flexible in scheduling injections or accommodating walk-ins for injections. However, it should be stressed that the doses should be given within the FDA dosing recommendation of 7 days before or after the scheduled LA CAB/RPV injection date.
- If LA CAB/RPV injections are missed or delayed by >7 days, suppressive bridging oral ART should be started and continued until LA CAB/RPV injections can be resumed. See Interruption of Antiretroviral Therapy and Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for additional considerations.
- As for all people with HIV, HBV status should be evaluated before the initiation of LA CAB/RPV (see Hepatitis B Virus/HIV Coinfection and Optimizing Antiretroviral Therapy in the Setting of Viral 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.
- 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.
- Because depressive disorders have been associated with LA CAB/RPV, people with SUDs also should be screened for depressive disorders and treated for depression if indicated.[37] If depressive disorders worsen while on LA CAB/RPV, reevaluation should occur to determine whether continued therapy with this regimen is advisable.

Importantly, additional research is 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.

Impact of Commonly Used Substances 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, cannabis and 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. People with HIV and SUDs should be offered evidence-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment) as part of comprehensive HIV care in clinical settings (see Table 15) **(AI).** ASAM provides resources and guidelines to aid clinicians in the management of SUDs.

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%).[38,39] 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.[39] Unhealthy alcohol use includes a spectrum of consumption, including at-risk or hazardous use, heavy episodic use (binge drinking), and alcohol use disorder (AUD).[40]

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.[41-43] In a meta-analysis of 27 studies, any alcohol use, unhealthy alcohol use, and alcohol use in sexual contexts were all associated with condomless sex among people with HIV.[42]

In addition, unhealthy alcohol use has been associated with interruptions in all steps of the HIV care continuum, including lower adherence to ART.[44,45] 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.[46-48] 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.[49-51] Studies also have demonstrated an association between unhealthy alcohol use and the loss of durable viral suppression,[52-54] greater time spent with a viral load >1,500 copies/mL after ART initiation,[55] increased risk of viral rebound, lower retention in care,[56,57] and increased mortality.[58-61] 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[62,63] and increase the risk of frailty in older people with HIV. 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, tuberculosis, and several cancers (e.g., liver, head and neck, and breast cancers).

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 and pharmacological treatments for unhealthy alcohol use among people with HIV demonstrate a small but significant reduction in alcohol use[64-66] (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]). 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,[67,68] 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.[69] In a randomized placebo-controlled trial of 100 people in prison 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%).[68]

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 HIV and AUD treatments also may improve the likelihood that a person with HIV will achieve viral suppression on ART. A randomized controlled trial of 128 people with HIV and AUD compared an integrated stepped-care model of alcohol treatment in Veterans Administration HIV clinics to traditional HIV care. 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 significantly associated 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).[70]

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, which are based on Child-Pugh classifications.

Benzodiazepines

Epidemiology

Although 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.[71] 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.[72]

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 engaging in transactional sex, sharing injection equipment with more people, and performing more frequent injections.[73] 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.[74] 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.[75] 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.[76] Benzodiazepines also may be used illicitly to counteract the negative side effects of stimulants, such as cocaine and methamphetamine.[77]

Management of Benzodiazepine Use

Repeated use of benzodiazepines can result in physiological 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. The Joint Clinical Practice Guideline on Benzodiazepine Tapering from ASAM provides recommendations for tapering strategies for different benzodiazepines.

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 or lenacapavir (LEN), their half-lives and concentrations can increase significantly, leading to enhanced and prolonged sedating effects. See the Liverpool HIV Drug Interaction Checker for available data on benzodiazepine-related interactions.

Cannabis and Cannabinoids

Epidemiology

Both medical and non-medical cannabis (marijuana) use are prevalent among people with HIV.[78] Cannabis belongs to a class of compounds that activate cannabinoid receptors.[79] This class, known as cannabinoids, also includes synthetic compounds, such as K2. Since the early 2000s, 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.[80] These compounds most commonly cause tachycardia, agitation, and nausea, but they have a wide range of psychiatric effects, including psychosis and paranoia.[81]

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.[82] 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.[83] However, in the CNICS cohort, a multisite clinical cohort of people with HIV, increasing cannabis use was associated with more heavy episodic drinking days per month, more cigarettes smoked per day, and more than twice the odds of hazardous alcohol consumption.[84] Although 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.[85] Although the available data suggest that the use of marijuana is not associated with decreased adherence to ART,[86] data are lacking on the impact of synthetic cannabinoids on ART adherence.

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.[87-89]

Club Drugs

Epidemiology

Club drugs are recreational substances that have euphoric or hallucinogenic effects or that are used to enhance sexual experiences.[6] 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.[90] Club drugs include MDMA, GHB, ketamine, benzodiazepines (see the Benzodiazepines 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).

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.[90-92]

Management of Club Drug Use

Treatment strategies for club drug use have not been well studied in controlled trials.[93] 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.[91,92] Overdoses secondary to interactions between club drugs (i.e., MDMA or GHB) and protease inhibitor–based ART have been reported.[92,94] For instance, using PDE5 or ketamine concurrently with CYP3A4 inhibitors, such as RTV, COBI, or LEN, can potentiate the effects of these substances.[90]

Cocaine

See the discussion in the Stimulants section below.

Opioids

Epidemiology

Opioids remain a significant concern for people with HIV, both for HIV acquisition and as major contributors to morbidity and mortality. Overdose involving opioids is the leading cause of accidental death in the United States.[95] 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.[96] 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.[97,98]

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 illicitly. 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.[95] Methamphetamines and cocaine also have been combined with fentanyl, but at a lower rate than heroin.[99,100] 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,[101] and a more recent study suggested 79% in 2022,[102] additional work is needed to improve ART coverage in this population. Data on engagement in care remains mixed for people with HIV who inject drugs. 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 remain engaged in care; however, this engagement gap had closed by 2012, and the probabilities of both ART usage and viral suppression were similar in the later years of the cohort, regardless of drug injection status.[103] However, results from the CDC's Medical Monitoring Project suggest that engagement in care for people with HIV who inject drugs remains a challenge.[104]

Management of Opioid Use

The FDA has approved three medications for the treatment of OUD that can help decrease or eliminate opioid use, reduce opioid-related morbidity and mortality, and improve HIV clinical outcomes. These medications—collectively termed medications for opioid use disorder—include buprenorphine, methadone, and naltrexone (see Table 15 below). Buprenorphine and methadone are opioid agonists, whereas naltrexone is an opioid antagonist. Buprenorphine and naltrexone have both oral and LA injectable formulations and can be prescribed in the setting of routine HIV clinical care.[105] The requirement for specific training to prescribe buprenorphine was eliminated in 2022; any prescriber with a U.S. Drug Enforcement Administration registration can now prescribe buprenorphine (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.

Use of buprenorphine or methadone can lead to reductions in HIV transmission risk behaviors, psychosocial and medical morbidity related to OUD, and criminal behaviors. Both buprenorphine and methadone are cost-effective interventions at the societal level.[106] 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.[107] An open-label randomized trial comparing extended-release naltrexone and sublingual buprenorphine-naloxone found that extended-release naltrexone was harder to initiate. However, among participants who successfully initiated treatment, relapse rates were similar between medications.[108] 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 fewer doses of depot naltrexone.[68] Based on these data, methadone or buprenorphine generally are used as first-line agents for the treatment of OUD among people with HIV. Depot naltrexone can be used as an alternative treatment for people being released recently from prisons or jails when other options are not available.

Important pharmacokinetic (PK) interactions between these medications (particularly methadone) and certain ARV drugs are available in the Liverpool HIV Drug Interaction Checker. As the use of LA injectable medications for OUD and HIV expands, additional studies evaluating PK interactions between these drugs are needed.

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 randomized study assessed the effectiveness of extended-release naltrexone compared to buprenorphine or methadone as OUD treatment in 114 people with HIV, including its association with viral suppression. In a secondary analysis, stable housing, high school–level education or greater, and income stability were associated with a greater reduction in opioid use over time.[109]

Xylazine and Other Opioid Adulterants

The opioid drug supply continues to evolve rapidly, with many new adulterants entering the supply. 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.[110] Xylazine is a substrate of CYP3A4 and, as such, when used with an ARV regimen including a CYP3A4 inhibitor, such as RTV, COBI, or LEN, may lead to elevated levels and prolonged half-lives of xylazine.[111] For people with HIV who continuously use opioids in areas with high rates of xylazine-adulterated fentanyl or illegally manufactured fentanyl, 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.[112]

Medetomidine, an alpha-2 adrenergic agonist sedative, is more potent and longer acting than xylazine. Medetomidine has been detected in the illicit opioid supply in North America since 2021. The CDC reported an outbreak of overdoses in May 2024 in the Chicago area.[113] A report later in 2024 cited data that medetomidine had been found in illicit drug samples in 18 states and the District

of Columbia.[114] In 2026, the CDC reported that the prevalence of medetomidine continues to rise at an alarming rate.[115] The growing prevalence and medical complications associated with medetomidine warrant vigilance in caring for people with HIV using opioids. Like other alpha-2 adrenergic agonists, medetomidine use can cause sedation, bradycardia, and hypotension. Prolonged sedation following administration of naloxone should prompt consideration of medetomidine. Withdrawal can cause hypertension, anxiety, nausea, vomiting, and alterations in consciousness, which can require emergency or intensive care. Medetomidine is a CYP3A, 2D, and 2E substrate and thus has the potential for significant drug–drug interactions with inhibitors or inducers of these enzymes. The CDC has published recommendations for clinicians.[115]

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. Powdered cocaine is administered intranasally or intravenously, while freebase cocaine (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.[99,100] 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.[116-118] Methamphetamine use is more common among MSM,[119] and increased rates of cocaine use have been observed among ethnic and racial minorities and people with a history of incarceration.[120]

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.[121] Stimulant use is associated with neurocognitive impairment,[122] 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.[123-127] Stimulant use has been associated with poor HIV continuum of care outcomes, including suboptimal rates of ART adherence,[128,129] retention in care, and viral suppression.[130-132] 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.[133]

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).[134,135] Among people with HIV who use crack and opioids, medications for OUD may improve ART adherence and viral suppression.[136,137] Limited evidence indicates that some pharmacologic interventions (e.g., methylphenidate, modafinil, bupropion, naltrexone, mirtazapine)[138,139] 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 than with placebo; however, the overall response rate was low.[140] Two double-blind randomized placebo-controlled trials found that daily mirtazapine use in people with methamphetamine use disorder led to reduced methamphetamine-positive urine drug tests, with one trial also demonstrating reduced sexual risk behaviors[139] and the other demonstrating a reduced number of days with methamphetamine use.[141] No specific recommended pharmacotherapy exists to treat stimulant use disorder in people with HIV.

Several behavioral interventions for the management of stimulant use disorder in people with HIV 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 reduced engagement in sexual transmission risk behaviors.[142] Contingency management has been shown to be effective in decreasing stimulant use among people with HIV. A 12-week pilot study of weekly contingency management among 31 people with HIV and stimulant use disorder in an urban safety-net HIV clinic reported increases in tenofovir-reactive urine tests and stimulant-negative urine tests with the intervention.[143] At baseline, 55% of the participants had viral suppression. The viral suppression rate increased to 88% for the 26 participants who attended the post-intervention visit. The sustained effects of contingency management on the reduction of stimulant use and improvements in ART adherence and viral suppression are less clear.[117,144,145] The addition of a positive affect intervention to contingency management, compared with an attention control condition, decreased HIV viral load among gay, bisexual, and other MSM with HIV.[146] 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.[147] People with HIV who use stimulants benefit most from multidimensional interventions that target substance use, ART adherence, and risky sexual behaviors.[142]

Despite the challenges discussed above, people with HIV who use stimulants can achieve viral suppression with ART[132] 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%).[148] 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.[148] Although the majority of people who use tobacco in the United States still use combustible products, use of vaporized nicotine (electronic cigarettes or e-cigarettes) has remained prevalent, especially among young adults and people with HIV.[149,150] In one study of 7,431 people with HIV, use of vaporized nicotine was associated with patient-reported depression and panic symptoms, which may have important implications for quality of life.[151]

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.[152,153] 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.[152] 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.[154-156]

Managing Tobacco Use

To maximize the survival benefits of ART, clinicians should consider using evidence-based behavioral and pharmacological[157-159] cessation strategies when treating people with HIV who smoke tobacco (see the tools and recommendations provided by the CDC and U.S. Preventive Services Task Force and recent review).[160] These include (but are not limited to) advising the individual to quit smoking, using the five A's (ask, advise, assess, assist, and arrange), employing motivational interviewing, and referring them to a tobacco quitline. Pharmacotherapies for smoking cessation (nicotine replacement therapy [NRT], 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. Varenicline is a partial nicotine receptor agonist. In comparative studies, varenicline was more effective than bupropion in smoking cessation.[161,162] Clinical trials among people with HIV have found varenicline to be both effective and safe.[157,159] 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) than with placebo.[159] Although significant between-group differences were not observed after 24 weeks, these data support the use of varenicline among people with HIV. Varenicline and dual NRT (LA plus short-acting NRT) are more effective than single NRT or bupropion, although all of these increase tobacco abstinence.[160] Varenicline should be used in combination with relapse prevention strategies and other measures for long-term tobacco cessation. Electronic cigarettes are not FDA approved for the treatment of tobacco use disorder, and insufficient evidence is available to suggest that e-cigarettes reduce the risk of lung cancer compared with combustible tobacco products.

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 380 mg IM every 4 weeks	No significant interaction with ARV drugs expected.	Has the greatest efficacy of all FDA-approved medications for AUD.
Opioid Use Disorder			
Buprenorphine *or* **Buprenorphine/ Naloxone** (sublingual tablets)	Individualize dosing based on the person's opioid use. See product labels for dosing information.	Potential interaction of buprenorphine with ARV drugs that are CYP inhibitors or inducers. See the Liverpool HIV Drug Interaction Checker.	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.
Buprenorphine (subcutaneous injection)	Weekly or monthly subcutaneous injection available in various doses. See product label for dosing information.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See the Liverpool HIV Drug Interaction Checker.	Weekly and monthly formulations are different. Weekly doses cannot be combined to yield an equivalent monthly dose. Because buprenorphine initiation may carry a risk of relapse and subsequent overdose, providing naloxone is strongly recommend.
Methadone	Individualize the dose. People who receive higher doses (>100 mg PO per day) are more likely to remain in treatment.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See the Liverpool HIV Drug Interaction Checker.	QTc prolongation is a concern at higher doses. Methadone can be prescribed for OUD only by a licensed OTP.

Table 15. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction With ARV Drugs	Comments
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.
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).	Bupropion is a CYP2D6 inhibitor and a CYP2B6 substrate. See the Liverpool HIV Drug Interaction Checker.	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; IM = intramuscular; LPV/r = lopinavir/ritonavir; OTP = opioid treatment program; OUD = opioid use disorder; PO = orally; QTc = QT corrected for heart rate; RTV = ritonavir

Knowledge Gaps

- Research is needed to assess different strategies integrating SUD treatment and HIV treatment (e.g., telemedicine, artificial intelligence, decision tools) to improve the reach and effectiveness of evidence-based treatment for SUD and HIV.
- Implementation research is needed on how to deliver LA ART with LA treatment for SUDs to improve clinical outcomes of HIV and SUD.
- Research using an effectiveness-implementation hybrid trial design is needed to evaluate different strategies for improving HIV care continuum outcomes among people who use substances.
- More research is needed to assess PK interactions between ART and OUD treatments, including LA and short-acting formulations of both.

- Research is needed to determine whether viral suppression achieved through ART prevents transmission of HIV to needle/injection equipment-sharing partners, analogous to “treatment as prevention” for sexual partners.
- Research is needed to determine the preferred approaches for supporting ART adherence (including to LA ARV drugs) among people with HIV and SUDs.

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Transplantation in People With HIV

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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: o 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).** o 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).** o 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).** o 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 16 provides information regarding expected interactions based on available data and theoretical estimates. Safe and effective use of immunosuppressants should be guided by TDM.

Table 16. 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.
NNRTI	↔ NNRTI **With EFV, ETR, and NVP** • ↓ Immunosuppressant expected	Initiate standard doses and adjust based on TDM. **With EFV, ETR, and NVP** • May need higher doses	Initiate standard doses and adjust based on TDM. **With EFV, ETR, and NVP** • May need higher doses	Initiate standard doses and adjust based on TDM. **With EFV, ETR, and NVP** • May need higher doses.

Table 16. Drug Interactions Between Antiretroviral Drugs and Immunosuppressants Used Post-Transplant

	Overview of Interaction Potential	Tacrolimus	Sirolimus	Cyclosporine
	With DOR (A Weak Inducer) • ↓ Immunosuppressant possible **With RPV** • ↔ Immunosuppressant	**With RPV** • Monitor QTc with RPV.	**With RPV** • Monitor QTc with RPV.	**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.

Table 16. Drug Interactions Between Antiretroviral Drugs and Immunosuppressants Used Post-Transplant

	Overview of Interaction Potential	Tacrolimus	Sirolimus	Cyclosporine
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.
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 using the Liverpool HIV Drug Interaction Checker. The table below is not comprehensive and is meant to highlight commonly used drug classes in transplant recipients with HIV.

Table 17. 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

Table 17. Drug Interactions Between Antiretroviral Drugs and Medications Commonly Used in Transplant Recipients

Drug Class	Examples	Effects of Interactions
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
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 the Liverpool HIV Drug Interaction Checker 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 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 A, Tables 1–10). 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.

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 16). 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

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Panel's Recommendations
Antiretroviral Therapy for Women With HIV
• 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).**
• A pregnancy test should be performed for women of reproductive potential before initiation of ART **(AIII).** Clinicians should discuss intentions regarding pregnancy with all women of reproductive potential.
• When selecting or evaluating an ARV regimen for women who are considering pregnancy, 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).**
• Drug interactions between ART and hormonal contraceptives and hormone replacement therapy are less of a concern with second-generation INSTI-based regimens than some other ARV drugs. When prescribing ARV regimens for women with HIV, clinicians should consider the potential for PK interactions between ARV drugs and with hormonal contraceptives **(AII)** and hormone replacement therapy. Refer to the Liverpool HIV Drug Interaction Checker for a summary of available data and recommendations when selecting ARV and hormone combination therapy.
• Weight gain after initiation of ART occurs in most patients. Some studies suggest increased weight gain in women, particularly among Black women. ART initiation or switch should not be delayed due to concern for weight gain, and shared decision-making should inform ARV choices.
Antiretroviral Therapy During Pregnancy
• All women with HIV should initiate ART before or early in pregnancy for their own health and for the prevention of perinatal HIV transmission and transmission of HIV to sexual partners **(AI).**
• During pregnancy, an additional goal of ART is to maintain a viral load below the limit of detection throughout pregnancy 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 of each agent during pregnancy. The benefits and risks of specific ARV regimens during pregnancy should be discussed with all pregnant women **(AIII),** and clinicians should consult the Perinatal Guidelines when designing a regimen**.**
Antiretroviral Therapy Postpartum
• ART should be continued postpartum **(AI).**
• Counseling on infant feeding options should be provided to all postpartum women.
• Clinicians should support maternal ART adherence for women with HIV and viral suppression (<50 copies/mL for at least 3 months) who choose to breastfeed (see Adherence to the Continuum of Care).
• Breastfeeding **is not recommended** for women who are not virally suppressed or for those who develop a detectable viral load (≥50 copies/mL) while breastfeeding. See the Perinatal Guidelines for detailed recommendations.
Special Considerations for Menopause and Comorbidities
• Preferred ARV regimens are the same for menopausal women with HIV as for other populations **(AIII).**
• Counseling and consideration of menopausal symptoms and comorbidities common among women in menopause—including cardiovascular disease, weight gain, neurocognitive decline, bone loss, and depression—should be a part of comprehensive HIV care.

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*

Key: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitor; PK = pharmacokinetic

Introduction

This section outlines key clinical and therapeutic considerations and basic principles related to antiretroviral (ARV) drug use in women with HIV. Clinicians should consult the Perinatal Guidelines for a more in-depth discussion regarding preconception counseling and care during pregnancy and in the postpartum period. Historically, women have represented the minority of participants in registrational trials of antiretroviral therapy (ART) and in studies of specific regimens and their associations with comorbid conditions.[1] Where available, evidence for differences between men and women from comparative trials or observational cohort data for efficacy and safety from trials done in women and specific risks or therapeutic considerations in women across the reproductive lifespan are discussed in this section.

Antiretroviral Therapy Considerations

In Women of Reproductive Potential

All women with HIV who are of reproductive 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 the importance of ART in 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 regularly discuss intentions regarding pregnancy with all women of reproductive potential. A pregnancy test should be performed before initiating ART **(AIII).**

Before initiating ART in a woman of reproductive potential, clinicians should review the What to Start: Initial Combination Antiretroviral Regimens for People With HIV section and the Perinatal Guidelines for information to consider when choosing an ARV regimen. For information on the safety and efficacy of different ARV drugs during pregnancy, please review the Perinatal Guidelines.

For women with HIV who are planning to conceive, ART should be initiated and viral suppression achieved before pregnancy whenever possible. Women with HIV 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 the Antiretroviral Counseling Guide for Health Care Providers in the Perinatal Guidelines).

For women with HIV who are not planning to conceive, but who may become pregnant, please see *Recommended Initial Regimens for Most People With HIV* and *Initial Antiretroviral Regimens for Certain Clinical Scenarios*. Clinicians should also refer to the Perinatal Guidelines for recommendations.

For women with HIV who are pregnant, please review the Pregnancy section below and the Perinatal Guidelines for more detailed discussion about ART use during pregnancy and postpartum.

In Women Who Are Not of Reproductive Potential

Some women with HIV do not have the potential to conceive because of medical, surgical, or other factors (e.g., they do not have a uterus, ovaries, or fallopian tubes or because they are postmenopausal). Recommendations for ART are the same as for other people with HIV (see What to Start, Optimizing Antiretroviral Therapy in the Setting of Viral Suppression, and Virologic Failure). However, there are still some important sex differences to consider, as described below.

Sex Differences in Antiretroviral Therapy

In general, studies to date have not shown sex differences in virologic responses to ART.[2-7] However, limited data show that pharmacokinetics (PK) of some ARV drugs may differ between men and women, possibly due to variations in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P450 activity, drug transporter function, and excretion activity.[7-11]

Adverse Effects

In general, currently available ART regimens are efficacious in both men and women. There is uncertainty about the specific risks of adverse effects in women due to lack of sufficient data.[12]

Several studies with older ARV drugs have suggested that sex may influence the frequency, presentation, and severity of some ARV-related adverse events.[13-15] Sex differences in adverse effects–related discontinuation rates of integrase strand transfer inhibitors (INSTIs) have also been reported.[16] In the ICONA cohort, ART-naive and ART-experienced women with HIV treated with dolutegravir (DTG)-based regimens had a higher risk of toxicity-related discontinuation compared with men through up to 4 years of follow-up.[17] A subsequent systematic review and meta-analysis of 15 observational DTG studies that included 7,506 women reported higher odds of DTG discontinuation due to side effects in women than in men; however, no sex differences in neuropsychiatric side effect–related discontinuations were observed.[16] It is unclear whether this difference is a class effect, because an older study reported higher discontinuation rates of non-INSTI-based regimens in women compared to historical studies in men.[18]

Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and some ARV drugs.[19-22] ARV regimens that contain tenofovir disoproxil fumarate (TDF), boosted protease inhibitors, or both are associated with a significantly greater loss of bone mineral density (BMD) than regimens that contain other nucleoside reverse transcriptase inhibitors or raltegravir (RAL).[23-26] Clinicians should consider avoiding TDF if possible in women with HIV who have high risk for osteoporosis and fracture. Recommendations for the management of bone disease in people with HIV have been published.[27]

Weight Gain and Antiretroviral Therapy

Weight gain is common after initiating ART, and decisions regarding ART regimens should be centered on optimization of viral suppression (see Weight Gain in People With Treated HIV). Selection of ART regimens either for initiation or switch should not be guided by whether a particular medication will prevent or decrease weight gain. The mechanisms underlying differences in ART-associated weight gain remain unclear, including differences with particular regimens and differences by sex. Clinicians should have informed discussions with people with HIV, especially women, regarding the potential for weight gain with ART initiation or switch as part of shared decision-making. Counseling weight management strategies should be a part of comprehensive HIV care. 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 INSTI-based regimens (DTG and bictegravir). In a pooled analysis of eight

randomized controlled trials with ARV-naive people initiating ART, female sex was associated with approximately 50% higher odds of a ≥10% weight gain compared with male sex (17.4% vs. 12.2%), with Black females being significantly more likely to experience a ≥10% weight gain than non-Black females (19.7% vs. 12.4%).[28] At 144 weeks of follow-up in the ADVANCE study, a 12.3-kg weight gain was recorded among women receiving tenofovir alafenamide (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.[29] 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 when compared to 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.[30-32] In the Women's Interagency HIV Study (WIHS), 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).[31] 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. In an observational study of women with HIV and viral suppression, 419 women who switched to an INSTI-based regimen (47% switched to second-generation INSTIs) were compared to 712 women who did not switch. There was a significantly faster increase in waist circumference per 6 months in the INSTI group compared to the non-INSTI group when the switch occurred in late perimenopause and menopause. This difference was not observed in the premenopausal participants. Although there were significantly higher proportions of participants on TDF and EFV in the non-INSTI group, the finding of increases in waist circumference in the INSTI group remained in sensitivity analyses restricted to participants on TDF and when participants on EFV were excluded.[33]

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.[34] The extent of TAF-associated weight gain may be affected by baseline body mass index (BMI). Among participants of the WIHS cohort, weight and BMI rose among women with baseline BMI <30 kg/m^2 when transitioning to INSTI, TAF, or INSTI and TAF together.[35]

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, substantial uncertainty continues as to whether INSTIs are causing weight gain or whether the comparator drugs are suppressing weight gain.[36] 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.

Adherence to Antiretroviral Therapy

Several U.S. studies have demonstrated lower rates of ART adherence among women compared with men. CDC data from the Medical Monitoring Project show that only about 60% of women reported perfect adherence over the prior 30 days between 2015 and 2019.[37] Large observational studies using Medicare claims and commercial databases similarly found that women had higher odds of nonadherence than men, whether measured by percent days covered or short-term dose recall.[38,39] A Canadian cohort showed that women were significantly less likely than men to maintain optimal adherence, even after adjusting for factors such as ethnicity and injection drug use.[40]

Multiple barriers contribute to adherence challenges in women with HIV. Women with low adherence are more likely to experience depression, alcohol use, and unmet social needs.[41] Access to food, housing, transportation, social support, and strong patient–provider relationships have been linked to

better adherence.[42-44] Structural factors including poverty, transportation challenges, limited health literacy, and gaps in insurance coverage also explain part of the racial disparities in adherence among women.[45] Age plays a role as well: Women aged 50 and older tend to have better adherence than younger women,[36] yet menopausal symptoms are common and are associated with poorer adherence.[37,38] Despite nearly 70% of older women reporting menopausal symptoms, only a small proportion receive treatment for these symptoms. It is possible that addressing these symptoms may help improve adherence to ART.[38,39]

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 or treatment interruption, which may lead to viremia. The addition of pre-exposure prophylaxis for the partner without HIV in such situations will further reduce the risk of HIV transmission. Both partners should be screened for sexually transmitted infections (STIs) and receive appropriate treatment if STIs are diagnosed.

Considerations for Women of Reproductive Potential Who Are Not Planning to Conceive

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 women with HIV of reproductive potential. These women 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. Women 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 (DDIs) as discussed below (also see the Perinatal Guidelines).

Drug–Drug Interactions Between Hormonal Contraceptives and Antiretroviral Drugs

The widespread use of second-generation INSTI-based regimens has decreased the potential for clinically significant DDIs with hormonal contraceptives. However, interactions that may reduce contraceptive efficacy remain a concern with select nonpreferred ARV drugs. Predicting the clinical implications of these interactions is challenging, as most data are from short-duration PK studies in healthy volunteers, and clinical data in women with HIV are limited. The magnitude of change in drug concentrations that may reduce contraceptive efficacy or increase adverse effects is also not known for all forms of contraceptive.

When prescribing ARV regimens for women with HIV, clinicians should consider the potential for PK interactions between ARV drugs and with hormonal contraceptives **(AII).** Concerns about PK interactions 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 the chosen hormonal contraceptive and select ARV regimens, particularly those containing EFV, cobicistat (COBI), or ritonavir (RTV). When appropriate, the interacting ARV drug may be switched to an effective alternative with lower interaction potential

based on ARV history and prior resistance testing results (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression). A summary of key contraceptive interactions with select ARVs is listed below and also in Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives in the Perinatal Guidelines. Clinicians are encouraged to check for DDIs by using the Liverpool HIV Drug Interaction Checker.

Cobicistat- and Ritonavir-Containing Regimens: These pharmacokinetic boosters present a complex interaction profile. The concomitant use of COBI- or RTV-containing regimens with drospirenone-containing contraceptives should be avoided due to the increased risk of hyperkalemia.[50] While these PK boosters can decrease estrogen levels (potentially causing spotting), they tend to increase progestin exposure, which generally preserves contraceptive effectiveness.[51,52] The increase in progestin exposure does not necessitate a dosage adjustment; however, women with HIV using these combinations should be monitored for progestin-related adverse effects.

Efavirenz: EFV significantly decreases the concentration of progestins delivered by most hormonal methods, including combined oral contraceptives, vaginal rings, progestin-only pills, and contraceptive implants.[51,52] This reduction creates a risk of contraceptive failure, and these methods are generally not recommended for use with EFV-based regimens. Injectable depot-medroxyprogesterone acetate (DMPA) is a notable exception, as a significant reduction in medroxyprogesterone acetate exposure has not been described with EFV. No change in DMPA dose or frequency is necessary.

Hormonal Contraceptives Considerations in Adolescents

In adolescents, there may be concerns about the impact of long-term DMPA use on bone health with or without coadministration of ART, specifically TDF. These concerns should not preclude the use of DMPA as an effective contraceptive unless clinical evidence indicates bone fragility. Refer to Special Considerations for Antiretroviral Therapy Use in Adolescents With HIV in the Pediatric Guidelines for more information.[51-57]

Pregnancy

All women with HIV should initiate ART before or early in pregnancy for their own health and for the prevention of perinatal HIV transmission and transmission of HIV to sexual partners **(AI).** Effective ART reduces the risk of perinatal HIV transmission by decreasing maternal viral load in blood and genital secretions.[58-60] Clinicians who are caring for pregnant adults and adolescents with HIV should review the Perinatal Guidelines for more detailed discussions.

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 pregnant women 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 **(AIII).** 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 pregnant women should be individualized according to specific ARV history, the results of drug-resistance assays, and the presence of comorbidities, including hepatitis B coinfection, 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 viral suppression, COBI-containing regimens, including those with atazanavir, EVG, or DRV, **are not recommended** for initiation during pregnancy **(AII).**[61] 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 **(BIII).** Alternatively, another regimen that is expected to maintain viral suppression can be used for the duration of the pregnancy.

Because evidence on the safety, efficacy, and pregnancy outcomes of long-acting injectable cabotegravir and rilpivirine (LA CAB/RPV) during pregnancy remains insufficient, no recommendation can be made for or against its use at this time. Data from case reports and PK modeling studies of women who became pregnant while receiving LA CAB/RPV suggest that monthly LA CAB/RPV dosing maintains CAB concentrations required for antiviral efficacy, but every-2-month dosing requires further study.[62-64] RPV dosed monthly and every 2 months may not maintain adequate levels for antiviral efficacy. In some reports, viral suppression was maintained in women who continued LA CAB/RPV during pregnancy, and no fetal adverse effects were observed.[62-66] For women already maintained on LA CAB/RPV at the start of pregnancy, counseling regarding the limited data of this regimen should be provided. Shared decision-making should inform these discussions and decisions regarding ART regimens. Options include switching to one of the recommended oral regimens during pregnancy or continuation of LA CAB/RPV with close viral load monitoring (every 1–2 months). In women with HIV who have barriers to oral ART and who are taking LA CAB/RPV and have viral suppression at the start of pregnancy and maintained during pregnancy, continuation of monthly LA CAB/RPV or switching from every-2-month to monthly dosing during pregnancy can be considered (see the Perinatal Guidelines).

To reduce the risk of perinatal HIV transmission, intravenous zidovudine during labor is recommended for pregnant women with HIV RNA that is unknown or ≥1,000 copies/mL near delivery, or those with known or suspected lack of adherence since the last HIV RNA result, regardless of 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 women with HIV are strongly encouraged to report cases of prenatal exposure to ARV drugs 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 **(AI).** 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.[67-69] 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 a long-acting (LA) reversible contraceptive—such as an implant or IUD—is desired, 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. Women with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about their desired approach to infant feeding. Replacement feeding with properly prepared formula or pasteurized donor human milk eliminates the risk of postnatal HIV transmission to the infant. Clinicians should support maternal ART adherence for women with HIV and viral suppression (<50 copies/mL for ≥3 months) who choose to breastfeed. Refer to the Perinatal Guidelines for additional considerations to minimize risk of transmission.

Breastfeeding is **not recommended** for women who are not virally suppressed or for women who develop a detectable viral load while breastfeeding because of concern for increased risk of HIV transmission through breast milk **(AI).**[70] 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.[71] Evidence suggests that women with HIV are reaching menopause at earlier ages than women who do not have HIV.[72,73] The WIHS cohort, 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 use of hormone replacement therapy (HRT), with rates of 14%, 16%, and 7%, respectively.[74]

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 virus (HCV) coinfection were associated independently with menopause at <45 years of age.[75] 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 HCV, and CD4 T lymphocyte (CD4) count <50 cell/mm^3 were significantly associated with an earlier age of natural menopause.[76]

In general, the recommendations for the use of ART in menopausal women are the same as for other populations. 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.[77] HIV confers a larger increase in relative risk of atherosclerotic cardiovascular disease (ASCVD), including incident myocardial infarction in women as compared to the impact of HIV on ASCVD risk in men.[78-80] In addition, ASCVD risk scores underpredict risk for cardiovascular events in people with HIV, with greater underprediction observed among women than men.[81] Because increased age and menopause are both risk enhancers for cardiovascular disease (CVD), this period is a critical time for CVD risk prevention strategies. Prevention strategies may include avoidance of ART regimens associated with increased cardiovascular risk (e.g., abacavir) and initiation of statin therapy. Attention should also be given to diabetes prevention;

faster increases in insulin resistance have been demonstrated in perimenopausal and postmenopausal women with HIV than women without HIV, regardless of ART regimen.[33,82]

Defining the relationship between HIV, menopausal symptoms, and mental health is complicated because symptoms from HIV itself, effects of ART, and other comorbidities may overlap. Some studies suggest that women with HIV experience a greater burden of vasomotor symptoms, sexual dysfunction, and mood changes during menopause.[72,73,83] Other studies did not find differences between women with and without HIV.[84,85] Menopausal symptoms also have been associated with reduced adherence to ART and poor cognitive performance.[86-89]

No studies have shown evidence of estrogen deficiency (i.e., menopause) affecting CD4 count, plasma HIV viral loads, or response to ART.[90,91] Two small studies showed no difference in plasma levels of tenofovir and RAL between pre- and postmenopausal women.[92,93]

The use of HRT is low among women with HIV.[87] Data are limited on DDIs between ART and estradiol as part of HRT, and DDI data with ethinyl estradiol cannot be extrapolated to the estrogens used for HRT because of differences in metabolism. DDIs between HRT and ART are possible, particularly regimens containing COBI, RTV, protease inhibitors, and some NNRTIs. Clinicians are encouraged to check for DDIs by using the Liverpool HIV Drug Interaction Checker.

Knowledge Gaps

- More research is needed to assess sex differences in ART-related adverse effects, PK, adherence, aging, inflammation, and comorbidities.
- Research is needed on the interactions between LA ARV drugs and hormonal contraceptives and menopausal HRT.
- Research is needed among women of all ages—from adolescence to older adulthood—to evaluate the long-term safety and efficacy of newer ART, including LA injectables.
- More research is needed on the underlying mechanisms for weight gain in women with HIV taking ART and their impact on pregnancy outcomes, CVD, diabetes, and other age-related comorbidities.
- Research is needed to identify and implement the most effective strategies to support women's ART adherence and persistence throughout the lifespan.
- Research is needed on the impact of the use of pharmacologic interventions for ART-associated weight gain and related comorbidities in women.
- Research is needed on the effects of treatment of menopausal symptoms on ART adherence.

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ANTIRETROVIRAL USE IN THE CONTEXT OF COINFECTIONS

Hepatitis B Virus/HIV Coinfection

Updated: September 24, 2026
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Key Considerations and Panel's Recommendations

General Considerations

- For people with HBV/HIV, hepatitis A and C virus serologic tests should be performed **(AIII).**
- Because HBV/HDV coinfection has been associated with serious liver complications, people with HIV and chronic HBV should be tested for HDV infection **(AIII).** People with HIV and HBV/HDV should be referred to an expert in the management of viral hepatitis.
- HBV reactivation has been observed in people with HBV/HCV while receiving interferon-free HCV treatment. Therefore, all people initiating HCV therapy should be tested for HBV.
- People with HCV/HIV and chronic HBV should receive ART that includes TAF or TDF, or they should have entecavir added to their ART regimen before initiating HCV therapy **(AIII).** See Hepatitis C Virus/HIV Coinfection for further details.
- For more information on HBV/HIV management, see Hepatitis B Virus Infection in the Adult OI Guidelines.

For People With HBV/HIV

- At initiation or switch of ART, all people who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication **(AIII),** and the quantitative HBV DNA test should be repeated every 3–6 months to ensure effective HBV suppression.
- An ARV regimen for people with HBV/HIV should include (TAF or TDF) plus (3TC or FTC) as components of a fully suppressive ARV regimen **(AI).**
- In certain situations, TAF or TDF alone can be used as the only drug with HBV activity because it has efficacy for the treatment of HBV in people without HIV **(AIII).** TAF or TDF alone for HBV treatment should be used in combination with an effective ARV regimen. See text for details.
- Using 3TC or FTC as the only drug with HBV activity in an ART regimen **is not recommended (AII)** because HBV resistance to these drugs can emerge.
- If entecavir is used in people with HBV/HIV, it must be used in addition to a fully suppressive ARV regimen **(AII).**
- Discontinuation of agents with anti-HBV activity may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; anti-HBV therapy should not be stopped in people with HBV/HIV **(AII).**

Before Initiating Tenofovir-Sparing Antiretroviral Regimens

- People with HIV should have their HBV status verified before initiating a tenofovir-sparing ARV regimen. See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for details.

For People With HBV/HIV

- For people with HIV and positive HBsAg, anti-HBV therapy (TAF, TDF, or entecavir) must be given if the selected ARV regimen does not contain tenofovir **(AII).**
- TAF or TDF are preferred for HBV treatment due to their higher barrier to resistance for HBV. If TAF or TDF cannot be safely used, or there is a desire to avoid tenofovir, entecavir is the alternative HBV therapy **(AII).** If there is known HBV resistance to 3TC and/or entecavir, consult an expert in HBV treatment.

For People With HIV and Prior HBV Infection

- In people with HIV who test positive for anti-HBc and negative for HBsAg, monitoring for HBV reactivation is recommended if transitioning to tenofovir-sparing ART (regardless of anti-HBs level) **(BIII).** See text for details.
- For people with isolated anti-HBc, see the Immunizations for Preventable Diseases in Adults and Adolescents With HIV section of the Adult OI Guidelines for HBV vaccination recommendations.

For People Without Confirmed Protective Immunity to HBV

- In people with HIV who are anti-HBs and anti-HBc negative, HBV-active ART (e.g., TAF or TDF-containing ART) prevents incident HBV infection. Discontinuation of HBV-active ART in a person who lacks HBV immunity makes them vulnerable to HBV infection. HBV vaccination **is recommended** for all people with HIV without a protective level of anti-HBs (i.e., anti-HBs <10 mIU/mL) **(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*

Key: 3TC = lamivudine; ART = antiretroviral therapy; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ARV = antiretroviral; FTC = emtricitabine; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; OI = opportunistic infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Approximately 5% to 15% of people with HIV in the United States also have chronic hepatitis B virus (HBV) infection, defined as persistent HBV surface antigen (HBsAg) detected on two occasions at least 6 months apart.[1-3] The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in people with HBV/HIV than in people with chronic HBV without HIV.[4] Conversely, chronic HBV does not substantially alter the progression of HIV and does not influence HIV viral 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]

People who test positive for hepatitis B core antibody (anti-HBc) and who are HBsAg negative are considered to have prior HBV infection and are at risk of HBV reactivation; please see below for considerations before initiating tenofovir-sparing ART in this population. The Hepatitis B Virus Infection section in the Adult and Adolescent Opportunistic Infections (Adult OI) Guidelines also has more information.

Key Considerations for People With HBV/HIV

- People with HBV/HIV should be tested for hepatitis A virus (HAV) and hepatitis C virus (HCV) **(AIII).**
  - People without immunity to HAV should receive a full vaccination series **(AIII).** For details, see Immunizations for Preventable Diseases in the Adult OI Guidelines.
  - All people with HCV/HIV are candidates for curative HCV treatment and should be evaluated for HCV therapy (see Hepatitis C Virus in the Adult OI Guidelines). Because HBV reactivation has been observed in people with HBV during interferon-free HCV treatment,[15,16] people with HCV/HIV and chronic HBV should receive ART that includes tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) or should have entecavir added to a fully suppressive ARV regimen prior to initiating HCV therapy **(AIII).** A diagnosis of HBV reactivation should be considered in people with chronic HBV or a history of chronic HBV who experience elevated liver transaminases during or immediately after HCV therapy.

- A survey of people with HBV/HIV 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.[17] Because HBV/HDV coinfection has been associated with serious liver complications, people with HIV and chronic HBV should be tested for HDV infection **(AIII).**[18,19] 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 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 liver disease (see Hepatitis B Virus Infection in the Adult OI Guidelines). In addition, people with chronic HBV should be advised to abstain from alcohol, screened for alcohol use disorder,[20] and counseled on prevention methods that protect against both HBV and HIV transmission.[21]
- At ART initiation or switch, all people who test positive for HBsAg should be tested for HBV DNA by using a quantitative assay to determine the level of HBV replication **(AIII);** the test should be repeated every 3 to 6 months to ensure effective HBV suppression. See Hepatitis B Virus Infection in the Adult OI Guidelines or the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Practice Guideline for further monitoring guidance. The goal of HBV therapy is to prevent liver disease complications through the sustained 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.[22] The most common reason for persistent HBV viremia in people with HBV/HIV on TAF- or TDF-containing ART is suboptimal adherence; thus, the primary focus in this setting should be on improving adherence.[23]

Managing HBV/HIV Coinfection

The nucleotide reverse transcriptase inhibitors (NRTIs) TAF and TDF have potent activity against both HBV and HIV. TAF is a tenofovir prodrug with 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 people with HBV but without HIV was evaluated through two randomized controlled trials, including one that enrolled people with positive hepatitis B e antigen (HBeAg) and another that enrolled people with negative HBeAg. Both HBV treatment–naive and HBV treatment–experienced participants were eligible for enrollment. In these studies, TAF was non-inferior to TDF at 48 weeks of treatment (primary efficacy endpoint), based on the percentage of participants with HBV DNA levels <29 IU/mL (HBeAg-positive: 63.9% for TAF vs. 66.8% for TDF, adjusted difference –3.6% [95% confidence interval (CI), –9.8 to 2.6], $P = 0.25$; HBeAg negative: 94.0% for TAF vs 92.9% for TDF, adjusted difference 1.8% [95% CI, –3.6 to 7.2], $P = 0.47$).[28,29] Efficacy was sustained at 96 weeks of therapy. In a pooled safety analysis, people on TAF experienced significantly smaller mean percentage decreases in hip and spine bone mineral density than participants receiving TDF. The median change in estimated glomerular filtration rate (eGFR) also favored TAF.[25] After 3 years, participants were followed on open-label TAF. Decreases in eGFR and bone mineral density observed with TDF improved after switching to TAF.[30]

Lamivudine (3TC) was approved as monotherapy for treatment of HBV infection. However, because 3TC-resistant HBV emerges in approximately 40% and 90% of people with HBV/HIV after 2 years and 4 years on 3TC monotherapy, respectively, 3TC and emtricitabine (FTC) (based on its similarity with 3TC) should be used only in combination with other anti-HBV drugs **(AII).**[31]

Entecavir is a nucleoside analog with potent activity against HBV and weak activity against HIV. Using entecavir for HBV treatment without suppressive ART may result in selection of the M184V mutation that confers HIV resistance to 3TC and FTC.[32,33] Therefore, entecavir must be used in

addition to a fully suppressive ARV regimen **(AII).** 3TC resistance compromises the activity of entecavir against HBV. Entecavir **should not be used** in individuals with 3TC-resistant HBV. 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.

Recommended Therapy

An ARV regimen for people with HIV and HBV should include TAF or TDF plus 3TC or FTC as components of a fully suppressive ARV regimen **(AI).**[34-36] The decision of whether to use a TAF- versus TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and accelerated bone loss.

The ALLIANCE trial was a Phase 3, double-blind, randomized controlled non-inferiority trial that compared bictegravir/TAF/FTC to dolutegravir (DTG)/TDF/FTC in treatment-naive adults with HBV/HIV. The TAF-based regimen was non-inferior to the TDF-based regimen for both HIV-1 RNA and HBV DNA suppression at 48 weeks. TAF demonstrated significantly higher rates of HBeAg seroconversion at 96 weeks (32% vs. 15%, $P = 0.008$) with numerically higher rates of HBsAg loss (23% vs. 14%, $P = 0.07$), but this did not reach statistical significance.[37]

In a switch study in people with HBV/HIV, study participants who switched from a primarily TDF-based ARV regimen to the fixed-dose combination elvitegravir/cobicistat/TAF/FTC maintained or achieved HBV suppression with improved eGFR and bone turnover markers.[38] See Appendix B for guidance on renal dosing of NRTIs.

Important Considerations

- Discontinuation of HBV-active NRTI drugs may potentially cause serious hepatocellular injury resulting from the reactivation of HBV.[39] People with HBV/HIV should be counseled regarding the risks of HBV reactivation if treatment is discontinued.
- Islatravir (ISL) is **contraindicated** with 3TC and FTC due to reduced ISL-triphosphate concentrations, which may decrease ART effectiveness.[40] When an ISL-containing ARV regimen is used, TAF or TDF alone (without 3TC or FTC) or entecavir should be used for HBV treatment.
- In people with HBV/HIV, 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.[41]
- Increased transaminase levels in people with HBV/HIV may also indicate HBeAg seroconversion and may resolve with continued ART; thus, the cause of the elevations should be investigated before medications are discontinued. In people with increases in transaminase levels, HBeAg seroconversion should be evaluated by testing for HBeAg and hepatitis B e antibody (anti-HBe) (to assess for HBeAg loss and new anti-HBe antibody detection), as well as HBV DNA levels, which should decrease with immune reconstitution. Other causes of alanine aminotransferase (ALT) elevation—such as HCV or HDV infection, alcohol use, metabolic dysfunction–associated steatotic liver disease (MASLD), and hepatotoxicity from non-ARV or ARV agents—should also be considered.
- For drug–drug interaction guidance, see the Liverpool HIV Drug Interaction Checker.

Changing Antiretroviral Therapy in People With HBV/HIV

- **When switching or modifying an ARV regimen in people with HBV/HIV:**
  - The discontinuation of agents with anti-HBV activity may cause serious hepatocellular injury resulting from HBV reactivation hepatitis; anti-HBV therapy should not be stopped in people with HBV/HIV **(AII).**[39] Therefore, ARV drugs that are active against HBV (TAF or TDF in combination with 3TC or FTC) should be continued **(AII).**
  - If switching to a tenofovir-sparing regimen for HIV treatment, use TAF, TDF, or entecavir for HBV treatment (in addition to the tenofovir-sparing ARV regimen). People with HBV/HIV were generally not included in clinical trials that evaluated NRTI-sparing or NRTI-limited regimens. Anti-HBV therapy (TAF, TDF, or entecavir) must be given if the selected ARV regimen does not contain tenofovir (e.g., DTG/rilpivirine [RPV], long-acting cabotegravir/RPV, DTG/3TC, doravirine/ISL) **(AII).** See HBV Treatment When Using Tenofovir-Sparing Antiretroviral Regimens in People With HBV/HIV for further information.
  - In people with prior 3TC exposure without concomitant TAF or TDF, TAF or TDF is preferred **(AII)** because of the risk of HBV resistance to 3TC (and thus risk of reduced activity of entecavir) and the lower barrier to resistance for entecavir. Entecavir **should not be used** in individuals with 3TC-resistant HBV.
- **Monitoring people with HBV/HIV who are not on HBV-active therapies** (e.g., if TAF, TDF, or entecavir must be discontinued or cannot be used):
  - If HBV-active treatment is interrupted, careful monitoring for HBV reactivation is recommended,[39] with frequent testing of liver transaminases, especially in people with marginal hepatic reserve, such as those with compensated or decompensated cirrhosis **(AIII).** See Hepatitis B Virus Infection in the Adult OI Guidelines for more information.
- **For people with functional cure:**
  - For people with HBV/HIV who experience HBsAg loss that is maintained over 6 months (i.e., functional cure), insufficient evidence currently exists to guide decisions to switch to a tenofovir-sparing regimen. The risk–benefit of potential HBV reactivation should be considered if HBV-active ARV drugs are withdrawn, especially in people with severe liver disease, where the risk of fulminant liver failure is high in the setting of HBV reactivation hepatitis. Tenofovir-sparing regimens may be considered without addition of entecavir in people without significant liver disease. A period of monitoring for reactivation is recommended if HBV-active therapy is withdrawn. See Hepatitis B Virus Infection in the Adult OI Guidelines for further information.

HBV Treatment When Using Tenofovir-Sparing Antiretroviral Regimens in People With HBV/HIV

Several effective ARV regimens are available that do not include tenofovir. When using one of these regimens, the HBV treatment options include adding TAF, TDF, or entecavir to the ARV regimen. TAF or TDF alone can be used as the only drug with HBV activity, as it has efficacy for the treatment of HBV in people without HIV **(AIII).**[24,25] TAF or TDF are preferred over entecavir for HBV treatment because they have a higher barrier to resistance.

If TAF or TDF cannot be safely used or if there is a desire to avoid tenofovir**,** entecavir is the alternative HBV therapy **(AII)**[42,43]; entecavir must be used in addition to a fully suppressive ARV regimen when given to people with HBV/HIV **(AII).**[33] If there is known HBV resistance to 3TC and/or entecavir, consult an expert in HBV treatment**.**

In people with a history of 3TC use without concomitant TAF or TDF, TAF or TDF is the preferred HBV treatment over entecavir **(AII)**[44] due to the risk of HBV resistance to 3TC (and thus risk of reduced activity of entecavir) and the lower barrier to resistance for entecavir. If entecavir is used in this setting, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day (with renal dose adjustments for CrCl <50 mL/min).[42,45] However, since entecavir resistance may emerge, entecavir should be used with caution in such people, with frequent monitoring (approximately every 3 months) of HBV DNA levels to detect viral breakthrough.[33]

In people with known or suspected 3TC-resistant HBV, entecavir **is not recommended** because 3TC resistance reduces susceptibility to entecavir. Entecavir is currently **not recommended** during pregnancy (see Hepatitis B Virus Infection in the Adult OI Guidelines or the AASLD/IDSA Practice Guideline).

Considerations Before Initiating Tenofovir-Sparing Antiretroviral Regimens in People Not Known to Have Chronic HBV

HBV status should be evaluated in all people with HIV who are not known to have chronic HBV before the initiation of a tenofovir-sparing ARV regimen. See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for details. Considerations for screening include the following:

- In people with HIV without HBV, HBV-active ART prevents incident HBV infection.[46] Discontinuation of HBV-active ART in a person who lacks HBV immunity makes them vulnerable to HBV infection.
- For people with HIV without HBV and without HBV immunity (i.e., hepatitis B surface antibody [anti-HBs] <10 mIU/mL), vaccination should be initiated while considering tenofovir-sparing ARV regimens **(AII).**[47-50] For people with isolated anti-HBc, see Immunizations for Preventable Diseases in the Adult OI Guidelines.[46-50]
- People with HIV and prior exposure to HBV infection (negative HBsAg, positive anti-HBc, and either positive or negative anti-HBs) are likely at low risk (<2%)[51,52] of HBV reactivation and even lower risk of HBV reactivation hepatitis,[14] but insufficient studies exist to confidently estimate the risk in this population, and available estimates likely underestimate reactivation rates.
    - Of people with HIV and prior exposure to HBV infection, people with positive anti-HBs 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.[14,51,52]
    - In individuals with isolated anti-HBc, some experts prefer that HBV DNA be undetectable prior to switching to a tenofovir-sparing regimen (see Hepatitis B Virus Infection in the Adult OI Guidelines for more information).
    - Monitoring for HBV reactivation is recommended in individuals with positive anti-HBc and negative HBsAg who are transitioning to tenofovir-sparing ART (regardless of anti-HBs level) **(BIII).**[44,53] It is feasible to incorporate ALT monitoring into the frequent laboratory testing already (see the Laboratory Testing table). 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 or if clinically indicated. The timeline for reactivation is not clear in this population. ALT should be monitored every 1 to 3 months for the first 6 months and every 6 months thereafter, as recommended in the Hepatitis B Virus Infection section of the Adult OI Guidelines.

Knowledge Gaps

- Research is needed regarding optimal management strategies for people with HBV/HIV with ongoing HBV viremia despite HIV suppression, including strategies supporting adherence and add-on nucleoside therapy.
- Research is needed regarding the safety and efficacy of novel antivirals and immunotherapies to treat HBV in people with HBV/HIV.
- Research is needed to better understand how HIV, HBV, weight gain, MASLD, and alcohol and substance use interact to accelerate hepatic fibrosis and carcinogenesis.
- Research is needed to define which people with HBV/HIV can safely transition to tenofovir-sparing ART regimens, identify those at greatest risk for HBV reactivation, and determine optimal monitoring strategies after ART transition.
- Research is needed to define the utility of HBV vaccination for people with HIV and prior HBV exposure who are on tenofovir-sparing ART regimens.
- Research is needed to delineate implementation strategies to support continuous HIV/HBV treatment and HBV vaccination during transitions to tenofovir-sparing regimens, especially among different populations and in resource-constrained settings.
- Research is needed to address intersecting stigmas from HBV and HIV and how they impact treatment retention and clinical outcomes.

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Hepatitis C Virus/HIV Coinfection

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Panel's Recommendations
• All people with HIV should be screened for HCV infection **(AIII).** People at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected **(AIII).** • ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most people with HCV/HIV, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all people with HCV/HIV, regardless of CD4 cell count **(AI).** • Initial ARV regimens that are recommended for most people with HCV/HIV are the same as those recommended for people with HIV who do not have HCV. 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 people with HCV/HIV 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).** • People with chronic HCV/HIV should be screened for active and prior HBV infection by testing for the presence of HBsAg and anti-HBs and anti-HBc (total or immunoglobulin G). People who are not immune to HBV (i.e., anti-HBs <10 mIU/mL) should receive anti-HBV vaccination **(AIII).** • HBV reactivation has been observed in people with HBV during HCV treatment with direct-acting antivirals. Accordingly, before initiating HCV therapy, people with HCV/HIV and active HBV (positive HBsAg) should receive ART that includes TAF or TDF, or they should have entecavir added to a fully suppressive ART regimen 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*

Key: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

The treatment of hepatitis C virus (HCV) infection is rapidly evolving. People 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 people 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 people 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 people with HCV/HIV coinfection had a threefold greater risk of progression to cirrhosis or decompensated liver disease than people with HCV mono-infection.[8] The risk of progression is even greater in people with HCV/HIV who have low CD4 T lymphocyte cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in people with HCV/HIV, several studies have demonstrated that the rate of disease progression

continues to exceed that observed in people 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 medications, 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 currently in use.

Assessment of HCV/HIV Coinfection

All people with HIV should be screened for HCV infection **(AIII)** using sensitive immunoassays licensed for the detection of antibodies to HCV in blood.[15] People who are HCV-seronegative but at risk for HCV infection should undergo repeat testing annually or as clinically indicated. People who are HCV-seropositive should be tested for HCV RNA using a sensitive quantitative assay to confirm the presence of active infection. People who test positive for HCV RNA should undergo HCV genotyping and liver disease staging as recommended by the HCV Guidance.

- People with HCV/HIV should be counseled to avoid consuming alcohol.
- People with HCV/HIV also should be counseled about appropriate precautions to prevent transmission of HIV and/or HCV to others.
- People with chronic HCV/HIV 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 (anti-HBs) and hepatitis B core (anti-HBc; total or immunoglobulin G).
    - People with evidence of active HBV (positive HBsAg) 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 (i.e., anti-HBs <10 mIU/mL) should receive anti-HBV vaccination.
- People with HCV/HIV who are susceptible to hepatitis A virus (HAV) should be vaccinated against HAV.
- All people with HCV/HIV should be evaluated for HCV therapy and undergo assessment of liver fibrosis stage to predict subsequent risk of hepatocellular carcinoma and liver disease complications **(AIII).** See Hepatitis C Virus in the Adult OI Guidelines for details.

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

Initiation of ART for people with HCV/HIV should follow the recommendations for all people with HIV, 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 people also are recommended for people with HCV/HIV. Special considerations for ARV selection in people with HCV/HIV 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 people with HCV/HBV, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, before initiating HCV therapy, people with HCV/HIV and active HBV (positive HBsAg) should receive ART that includes tenofovir alafenamide or tenofovir disoproxil fumarate, or they should have entecavir added to their ARV regimen before initiating HCV therapy **(AIII).** See Hepatitis B Virus/HIV Coinfection for more details.
- People with cirrhosis should be evaluated for signs of liver decompensation according to the Child-Pugh classification system. All people 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 people with Child-Pugh class B and C disease (see Appendix B for ARV dosing in adults with hepatic insufficiency).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in people with HCV/HIV coinfection than in those with HIV mono-infection. Individuals with HCV/HIV 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 the upper limit of normal [ULN]) are typical in individuals with chronic HCV. 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. People 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 medications 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 people 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 direct-acting antiviral drugs are based on available pharmacokinetic interaction data or are predictions based on the known metabolic pathways of the agents. Whenever HIV and HCV drugs are used concomitantly, people 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 Liverpool HEP Drug Interaction Checker for updated information.

Note: Interactions with fosamprenavir, nelfinavir, and nevirapine are **not** included in this table because they are no longer commonly used and/or are not recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Please refer to the FDA product labels or the Liverpool HEP Drug Interaction Checker for information regarding drug interactions with these HIV protease inhibitors.

ARV Drugs	Individual Drug	Coformulated				
		May be used in mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C)		**May be used in mild hepatic impairment** (Child-Pugh class A) **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.	✓	✓

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				
		May be used in mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C)		**May be used in mild hepatic impairment** (Child-Pugh class A) **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**
Unboosted ATV	✓	✓	✓	✖	✖	✖
ATV/r or ATV/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]	✖	✖	✖
DRV/r or DRV/c	✓			✓ Consider monitoring for hepatotoxicity.[b] If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor for TDF-associated adverse events.[a]	✖	✖
LPV/r	✓			✖	✖	✖
TPV/r	✖	✖	✖	✖	✖	✖
DOR	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓
EFV	✓		✖	✖	✖	✖
ETR	✓		✖	✖	✖	✖
RPV 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				
		May be used in mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C)		**May be used in mild hepatic impairment** (Child-Pugh class A) **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**
DOR/ISL	✓	✓	✓	✓	✓	✓
BIC	✓	✓	✓	✓	✓	✓
CAB PO and IM	✓	✓	✓	✓	✓	✓
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.	✓ Consider monitoring for hepatotoxicity.[b] If used with TDF, monitor for TDF-associated adverse events.	✓ Consider monitoring for hepatotoxicity.[c] If used with TDF, monitor for TDF-associated adverse events.	✖
EVG/c/TAF/FTC	✓	✓	✓	✓ Consider monitoring for hepatotoxicity.[b]	✓ Consider monitoring for hepatotoxicity.[c]	✖
RAL	✓	✓	✓	✓	✓	✓
MVC	✓	✓	✓	✓	✓	✓

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				
		May be used in mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C)		**May be used in mild hepatic impairment** (Child-Pugh class A) **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**
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 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, people who are receiving voxilaprevir and pharmacologically boosted DRV or EVG should be monitored for hepatotoxicity.

[c] Glecaprevir exposures can increase when it is coadministered with EVG/c. Until more safety data in clinical settings become available, people 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**
↑ = Increase

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; ISL = islatravir; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; 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

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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 the Liverpool HIV Drug Interaction Checker 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 the Liverpool HIV Drug Interaction Checker 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 the Liverpool HIV Drug Interaction Checker).

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 Women 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 the Liverpool HIV Drug Interaction Checker 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 women: All women 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. The Liverpool HIV Drug Interaction Checker provides information on these interactions and 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 the Liverpool HIV Drug Interaction Checker 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 the Liverpool HIV Drug Interaction Checker 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

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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— o Changing ART to simplify dosing or to reduce side effects o Allowing flexible appointment scheduling o Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments o Linkage to resources to assist with unmet social and economic needs, such as transportation, food, housing, and other support services o 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, stigmatization, 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 Medications

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Adverse effects have been reported with all antiretroviral (ARV) medications. Commonly reported reasons for switching or discontinuing oral or injectable therapy were due to adverse effects, especially with the initiation of antiretroviral therapy (ART) regimens in the late 1990s and early 2000s.[1] Fortunately, newer ART regimens are associated with fewer serious and intolerable adverse effects. Generally, <10% of participants who are ART-naive and who enrolled in randomized trials of newer agents experience treatment-limiting adverse events.[2,3] However, the short-term and long-term complications of ART may be underestimated because most clinical trials use specific inclusion criteria that exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short (generally 2–4 years).

ART is recommended for all people with HIV regardless of CD4 T lymphocyte cell count, and with current treatments and approaches/strategies, therapy must be continued indefinitely. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART adverse effects must be anticipated and managed. From a safety and tolerability standpoint, the focus of management has evolved from identifying and managing toxicities related to early ARVs to individualizing therapy to avoid or mitigate long-term adverse effects, such as atherosclerotic cardiovascular disease, diabetes and other metabolic complications, kidney dysfunction, neuropsychiatric events, and accelerated declines in bone mineral density.

Antiretroviral Regimen Selection

When selecting an ARV regimen, clinicians must consider potential adverse effects and any prior history of drug intolerance. Additionally, several factors may predispose people with HIV to adverse effects of ARV medications. These factors include:

- 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[4,5] may increase the risk of hepatotoxicity when some protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).[6]
- Certain ARVs that may exacerbate pre-existing conditions. For example, psychiatric disorders may be exacerbated by efavirenz (EFV), rilpivirine, and, infrequently, by integrase strand transfer inhibitors.[7,8]
- Drug–drug interactions that may increase the toxicities of ARV medications or concomitant medications. For example, when pharmacokinetic boosters such as ritonavir or cobicistat are used.[9]
- Genetic factors that predispose people with HIV to some adverse effects of medications that are no longer commonly used in clinical practice, such as abacavir (ABC) hypersensitivity reaction,[10,11] EFV neuropsychiatric toxicity[9,12] or QTc (QT corrected for heart rate) prolongation,[13,14] and atazanavir (ATV)-associated hyperbilirubinemia.[15]
- Dosing errors, which can predispose people with HIV to adverse effects when medications are administered at incorrect doses—whether at doses that are too high or at inappropriate intervals—and can increase the likelihood of adverse effects.

Management of Adverse Effects

ART-associated adverse effects can range from acute and potentially life-threatening to chronic and insidious. When people with HIV experience treatment-limiting toxicities associated with ART, selecting new ART regimens that pose either no or a lower risk of exacerbating the condition or contributing to further complications is warranted. Serious life-threatening effects (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV medications 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 medication for the presumed causative medication without interrupting ART. Chronic, non–life-threatening adverse effects (e.g., dyslipidemia) can be addressed either by switching the potentially causative medication for another medication or by managing the adverse effect with nonpharmacological interventions or pharmacologic interventions such as statins. Management strategies must be individualized for each person with HIV. When adverse effects occur during the use of long-acting injectable ARV drugs, management may be challenging due to the persistence of drug in the body over the course of many months to years. Oral lead-in regimens for cabotegravir plus rilpivirine are available to assess short-term tolerability.

Switching 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:

- Medical and complete ARV history, including prior virologic responses to ART
- All previous drug resistance test results
- Viral tropism (if maraviroc is being considered)
- HLA-B*5701 status (if ABC is being considered)
- Comorbidities
- Pregnancy status and the desire and/or ability to become pregnant or use contraceptives
- Hepatitis B virus (HBV) status. People 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
- Concomitant medications and supplements, considering any potential drug interactions with ARVs
- Cost to people with HIV and options for patient assistance programs if needed (see Cost Considerations and Antiretroviral Therapy)

For the first few months after an ART switch, the person should be closely monitored for any new adverse effects, and HIV viral load should be monitored to ensure continued viral suppression.

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 A. Drug Characteristics Tables.

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

This table focuses on antiretroviral (ARV)-associated adverse effects that a person may experience as a result of taking an ARV regimen. The attribution of adverse effects to individual ARVs is inherently limited by the absence of long-term monotherapy trials, making it difficult to delineate the specific contribution of each medication within the combination regimens. These limitations should be considered carefully when assessing causality, as adverse effects may be related to the ARV regimen as a whole rather than to any single component.

Adverse effects for ARV medications that are no longer on the market or are not commonly used in clinical practice (didanosine [ddI], fosamprenavir/ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, nevirapine, saquinavir/ritonavir, stavudine [d4T], tipranavir/ritonavir, zidovudine [ZDV]), with few exceptions, have been removed from this table. Clinicians should refer to the product labels or to the archived July 10, 2019, version of the Guidelines for information regarding the adverse effects associated with select older ARVs. Because some adverse effects may persist long after discontinuation of the older ARVs—such as d4T, ddI, zalcitabine, and ZDV—and people with HIV may still present with these long-lasting toxicities, these medications remain listed among the ARVs associated with adverse effects such as lipodystrophy and peripheral neuropathy.

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.

This table highlights the common and/or severe adverse effects by ARV class and for individual ARVs, when appropriate. For ARV class–specific adverse effects, the table provides relative comparisons among individual ARVs for each class effect. In some cases, the terms “no known effect,” “rarely observed” (for select severe effects), “not common or severe,” or “no or limited data” are used, especially for the entry inhibitor and capsid inhibitor classes, where the evaluation of safety is based mostly on uncontrolled and nonrandomized clinical trials. See Appendix A. Drug Characteristics Tables for additional information listed by ARV medication.

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Cardiovascular Effects	Cardiac Conduction Effects	No known effect	**RPV and EFV:** QTc prolongation **RPV:** QTc prolongation occurred at 3 and 12 times the recommended dose. Consider alternatives when coadministered with drugs with known risk of Torsade de Pointes.	**ATV:** PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	No known effect	**FTR:** QTc prolongation was seen at 4 times the recommended dose. Consider alternatives when coadministered with drugs with a known risk of Torsade de Pointes.	No known effect

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
	Cardiovascular Disease	**ABC:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in people with traditional CVD risk factors.	No known effect	**DRV/r:** Associated with cardiovascular events in some cohorts.	Not common or severe	No or limited data	No or limited data
Dermatologic Effects, Not Including Systemic Hypersensitivity Reaction	Rash	**FTC:** Skin hyperpigmentation	All NNRTIs	ATV, DRV	All INSTIs	MVC, IBA, FTR	Not common or severe
	Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	No known effect	EFV, ETR > DOR, RPV	Rarely observed with DRV and ATV	Rarely observed with BIC, CAB, and RAL	No or limited data	Not common or severe
Gastrointestinal Effects	Cholelithiasis	No known effect	No or limited data	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	No known effect	No known effect	No known effect
	Gastrointestinal Effects	**ZDV > other NRTIs:** Nausea and vomiting	Not common or severe	GI intolerance (e.g., diarrhea, nausea, vomiting)	**EVG/c:** Nausea and diarrhea	No known effect	Not common or severe

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Hepatic Effects	Hepatic Effects	**When TAF, TDF, 3TC, and FTC are withdrawn in people with HBV/HIV coinfection or when HBV resistance develops:** People with HBV/HIV coinfection may develop severe hepatic flares.	**EFV:** Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. **RPV:** Risk may be further increased in people with HBV or HCV coinfection.	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported. **ATV:** Jaundice due to indirect hyperbilirubinemia	**DTG:** Rarely observed, but risk may be further increased in people with HBV or HCV coinfection. **BIC, CAB, EVG/c, RAL:** Not common or severe	**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.	Not common or severe
Hypersensitivity Reactions, Not Including Rash Alone or Stevens-Johnson Syndrome	Hypersensitivity Reaction	**ABC: Contraindicated** if person is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks.	Rarely observed	No known effect	Rarely observed	**MVC:** HSR reported as part of a syndrome related to hepatotoxicity. **IBA:** HSR, including infusion-related reactions and anaphylactic reactions, were reported.	No known effect

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
		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. People should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.					
Injection Site Reactions	Injection Site Reaction	Not applicable	**RPV IM injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma. **When given with CAB IM, injection site pain:** RPV > CAB.	Not applicable	**CAB IM injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma. **When given with RPV IM, injection site pain:** RPV > CAB.	Not applicable	**LEN SQ injection:** Reported in 47–65% of people; reactions may include swelling, erythema, pain, nodules, inflammation, and induration. Nodules and induration may persist for months in some people. Injection site necrosis has been reported.

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Metabolic Effects	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 proximal tubulopathy and urine phosphate wasting. **TAF:** Associated with smaller declines in BMD than those seen with TDF.	No known effect	No known effect	Not common or severe	No known effect	No known effect
	Diabetes Mellitus and Insulin Resistance	**ZDV**	No known effect	Rarely observed	No known effect	No or limited data	No or limited data
	Dyslipidemia	**ABC:** ↑ TG and ↑ LDL **TAF:** ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) **TDF:** Associated with lower lipid levels than ABC or TAF.	**EFV:** ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-boosted PIs:** ↑ TG, ↑ LDL, ↑ HDL	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	No known effect	No known effect
	Lactic Acidosis	Reported with older NRTIs (e.g., d4T, ZDV, ddI), but not with ABC, 3TC, FTC, TAF, or TDF.	No known effect	No known effect	No known effect	No known effect	No known effect

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
	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-containing regimens; however, a causal relationship has not been established.	**Lipohypertrophy:** Trunk fat increase is observed with PI-containing regimens; however, a causal relationship has not been established.	**Lipohypertrophy:** Trunk fat increase is observed with RAL-containing regimens; however, a causal relationship has not been established.	No known effect	No known effect
	Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs, especially BIC and DTG, than with other drug classes. Greater weight increase has also been reported with TAF than with TDF and with DOR than with EFV.				No known effect	No known effect
Musculoskeletal Effects	Myopathy/ Rhabdomyolysis	ddI, D4T Rarely observed with ABC, TAF, or TDF.	No known effect	No known effect	Rarely observed	No known effect	No known effect

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Neuropsychiatric Effects	Nervous System/ Psychiatric Effects	**Peripheral neuropathy (can be irreversible):** Associated with history of exposure to ddI, ddC, or d4T.	**Neuropsychiatric events:** EFV > DOR, RPV > 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. **RPV:** Depression, suicidality, sleep disturbances **DOR:** Sleep disorders and disturbances, dizziness, altered sensorium; depression, suicidality, and self-harm	No known effect	Insomnia, depression, and suicidality have been reported with INSTI use, primarily in people with pre-existing psychiatric conditions.	Not common or severe	Not common or severe

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Renal Effects	Renal Effects/Nephrolithiasis/ 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 renal effect than TDF.	**RPV:** Inhibits Cr secretion without reducing renal glomerular function	**ATV:** 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 pharmacokinetic booster for DRV or ATV):** Inhibits Cr secretion without reducing renal glomerular function	**DTG, COBI (as a pharmacokinetic booster for EVG), and BIC:** Inhibits Cr secretion without reducing renal glomerular function	No or limited data	No or limited data

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; BMD = bone mineral density; CAB = cabotegravir; CI = capsid inhibitor; COBI = cobicistat; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; 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; MI = myocardial infarction; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; QTc = QT corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQ = subcutaneous; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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Cost Considerations and Antiretroviral Therapy

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Recommendations and Key Considerations
• The complexities of the U.S. health care system may require that the costs for ART, especially out-of-pocket costs for the person with HIV, be one of the considerations in regimen selection, because such expenditures can directly affect affordability, adherence, and treatment outcomes. • Health insurance and prescription drug coverage can directly affect clinical outcomes for people with HIV; changes to coverage can result in lapses in viral suppression and should be anticipated and avoided as best possible. • Providers should routinely assess the costs of ART borne directly by the person with HIV and be prepared to modify the regimen when those costs create a barrier to initiation, adherence, or continuation of therapy. Any cost-driven regimen change must be evaluated against the person's full antiretroviral history, prior virologic responses, documented or suspected drug resistance, risk of adverse effects, and the potency and durability of the proposed alternative regimen. Modifying an ART regimen for cost considerations must never compromise virologic efficacy or long-term treatment outcomes **(AIII).** • Clinicians encountering payer-driven barriers to a clinically indicated regimen should pursue available mechanisms for challenging coverage determinations, including peer-to-peer review, formal appeals processes, and referral to clinic-based pharmacy staff, benefits managers, or other available resources with experience in navigating HIV-specific coverage **(AIII).** • The Ryan White HIV/AIDS Program offers opportunities to access essential HIV medical and support services, including medication assistance, to minimize cost as a barrier to care for people with HIV who have lower incomes. • Both medical and nonmedical case management services can be used to identify and address cost-related barriers to ART by linking individuals to private and public funding sources. • Disengagement from care occurs more frequently during transitions in care and coverage (e.g., transitioning from pediatric to adult care; changing employment status; moving from one state to another; being released from incarceration; switching insurance, including to Medicare).
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*

Key: ART = antiretroviral therapy

Introduction

The clinical benefits, public health impact, and cost-effectiveness of HIV treatment are well established,[1-6] and increased uptake and utilization of antiretroviral therapy (ART) is one of the four pillars of the *Ending the HIV Epidemic in the U.S.* initiative.[7,8] However, ART is costly. A 2023 study estimated that the net Medicaid spending from 2007 through 2019 was $25 billion for 17 million 30-day supplies of antiretroviral (ARV) drugs.[9] Estimated annual spending—inclusive of statutorily required manufacturer rebates to offset federal and state costs of most outpatient prescription drugs dispensed to Medicaid beneficiaries—increased 178%, from $1.1 billion to $3.0 billion during this 12-year period. According to a study of risk-adjusted 2016 Medicare claims, total spending for Medicare beneficiaries with HIV receiving ART was 221% greater than for beneficiaries without HIV, largely driven by ARV medication expenses.[10] Since the initial inclusion of an ARV cost table in these guidelines in 2012, the cost of brand-name, first-line ARV regimens has increased by more than 30% from 2012 to 2018,[11] which is 3.5 times the rate of inflation for that same time period.

This section provides guidance on cost considerations related to HIV clinical care. Ideally, ART costs do not influence regimen selection. However, the complexities of the U.S. health care system, including those related to out-of-pocket costs to people with HIV, may necessitate their consideration in regimen selection, because expenditures may directly or indirectly affect adherence and virologic outcomes. Additionally, health insurance and prescription drug coverage determinations, based in part on ART costs, can directly affect clinical outcomes for people with HIV; the clinical impact of changes to insurance coverage is also discussed in this section. Overall costs to the health care system, insurers, and 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 understand cost considerations that may limit HIV care and the support services available to mitigate cost as a barrier to effective HIV treatment. The 2025 federal budget reconciliation law enacted several changes with direct implications for health coverage among people with HIV, including new Medicaid work requirements, mandatory semi-annual eligibility redeterminations, and cost-sharing requirements for Medicaid expansion enrollees; restrictions on Medicaid, Child Health Insurance Program, and Affordable Care Act (ACA) Marketplace eligibility for certain categories of lawfully present immigrants; and modifications to ACA Marketplace plan structures.[12-14] Enhanced ACA Marketplace premium tax credits, in effect since 2021, expired at the end of 2025, increasing premium costs for marketplace enrollees who had qualified for enhanced subsidies.[15,16] These pressures, compounded by rising ARV drug costs, increased enrollment, and decreased 340B rebate revenues, have prompted a number of AIDS Drug Assistance Programs (ADAPs) to implement cost-containment measures, including reductions in financial eligibility thresholds, enrollment caps, waiting lists, formulary restrictions, and changes to insurance premium assistance programs.[17] Providers should assess the current coverage status for people with HIV at each visit and be familiar with available assistance programs, as coverage transitions can disrupt continuity of ART and related care.

Health Care Coverage to Maximize Access to Antiretroviral Therapy

Health care access in the United States can vary, depending on factors such as 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 35% of people with HIV in the United States live in the 10 states that had not expanded Medicaid under the ACA as of March 2026, including Florida, Georgia, and Texas.[18,19]

The ACA and its Medicaid expansion have greatly improved insurance coverage among people with HIV.[20] Before the ACA, many individuals with HIV were denied insurance due to pre-existing condition exclusions and high costs. [21,22] Soon after implementation, the ACA and Medicaid expansion were associated with increased HIV testing and diagnoses, ART initiation and viral suppression, fewer hospitalizations among uninsured people with HIV, and improved awareness of HIV status.[23-26]

A retrospective analysis of North American AIDS Cohort Collaboration on Research and Design (or NA-ACCORD) data examined the associations between state Medicaid expansion associated with the ACA and HIV outcomes in the United States.[27] The study found that Medicaid expansion was associated with higher CD4 T lymphocyte (CD4) cell counts at enrollment; however, no significant benefit on viral suppression or other HIV care outcomes was observed. The authors suggest the null effect on downstream HIV measures may be due to the Ryan White HIV/AIDS Program (RWHAP), the highly cost-effective federal safety net program, potentially concealing HIV outcome deficits that might otherwise be apparent in states foregoing Medicaid expansion.[28] At the population level, Medicaid expansion could have a greater effect on reducing HIV incidence by increasing diagnoses and improving linkage to care.[29]

In a prospective study of 101 people with HIV who enrolled in expanded Medicaid in Nebraska in 2020 and 2021, viral suppression significantly increased from 58.4% to 77.2%, with concurrent improvements in access to care and reductions in cost-related ART dose-skipping and rationing.[30] Together, these studies underscore the impact of Medicaid expansion for HIV care access, even as the evidence on downstream care continuum outcomes remains mixed.

Changes or lapses in health insurance, commonly referred to as "coverage churn," are common and can result in interruptions in clinical care and viral suppression.[31] Among people with HIV, coverage churn has been associated with sharp increases in transmissible viremia and delayed return to viral suppression upon re-engagement in care.[32] Federal policy changes anticipated to take effect in 2026 and 2027, described above, could increase the frequency and scope of coverage disruptions for people with HIV.

Frequent recertification requirements for ADAPs or Medicaid can lead to lapses in ART use.[33-36] Providers should be aware of the certification needs for the states in which they provide care. Both ADAPs and Medicaid are administered at the state level; therefore, eligibility criteria and medication formularies differ from state to state. When people with HIV receiving Medicaid or ADAP ARV drug coverage move from one state to another, advanced planning is required to ensure uninterrupted access to ART. For example, specific ARVs covered by Medicaid may not be covered by the state ADAP (e.g., long-acting cabotegravir/rilpivirine [LA CAB/RPV]), potentially resulting in the need for regimen changes if a change from Medicaid to an ADAP is required.

Interruptions in health insurance and prescription drug coverage access are also common for people with HIV involved with the criminal justice system. While incarcerated, some people with HIV may be disenrolled from their health care insurance and prescription drug coverage. However, in 2023, the Centers for Medicare & Medicaid Services (CMS) released guidance for states when applying for a partial waiver of this policy, enabling coverage for services provided 30 to 90 days before release.[37] With approval of this waiver, states are expected to suspend (not terminate) Medicaid coverage during incarceration and must collaborate with correctional facilities to assist incarcerated individuals who are not currently enrolled in Medicaid with submitting applications during incarceration using presumptive eligibility. Minimum benefits expected by CMS in state waiver proposals include case management services for pre- and post-release (including linkage to outpatient HIV care), medication-assisted therapy for substance use disorders, and at least a 30-day supply of medications at release. Additionally, although federal RWHAP and ADAP funds cannot cover care and treatment for individuals in state or federal prison systems, they can provide short-term, transitional support to people with HIV in local correctional facilities (e.g., city or county jails).[38]

Utilization management strategies—including prior authorization requirements, step therapy protocols, and formulary restrictions—are applied by payers across coverage types, including commercial insurers and state Medicaid programs.[39,40] Medicare Part D plans and Medicare Advantage Plans offering Part D benefits, however, operate under a distinct and more protective regulatory framework: ARV medications carry protected drug class status, which requires coverage of all or substantially all approved agents, explicitly prohibits prior authorization and step therapy requirements, and specifies that any additional coverage restrictions must be consistent with these Guidelines.[41]

Although utilization management mechanisms are commonly used to manage drug expenditures at the population level, data on their application to ART are limited. Given the risks of viral rebound, drug resistance, and increased HIV transmission associated with treatment interruptions or delays in initiating preferred regimens, these strategies should be applied cautiously. Clinicians encountering payer-driven barriers to a clinically indicated regimen should pursue available mechanisms for challenging coverage determinations, including peer-to-peer review, formal appeals processes, and

referral to clinic-based pharmacy staff, benefits counselors, or other available resources with experience navigating HIV-specific drug coverage **(AIII).**[42]

Cost Sharing in the United States

Prescription drug pricing in the United States involves complex, largely confidential systems of discounts, rebates, and reimbursement rates that vary by state, purchaser, payer type, and the availability of generic competitors (see Table 21 below). As a result, providers may find it difficult to navigate cost-containment practices, such as formulary restrictions; prior authorization requirements; and cost-sharing arrangements, including copayments (a fixed dollar amount per prescription), coinsurance (a fixed percentage of the prescription cost), and deductibles.

Out-of-pocket costs for people with HIV can be prohibitive, creating a barrier to initiating, switching, and continuing 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, out-of-pocket costs may indirectly lead to worse health outcomes and an increased use of the medical system, especially among people with chronic diseases.[43-48] In 2022, the Centers for Disease Control and Prevention (CDC) Medication Monitoring Project (MMP) reported that less than 5% of people with HIV previously taking ART had stopped; however, among people in the MMP who were no longer taking ART, 34% reported that money or insurance problems were contributors to stopping ART.[49]

Conversely, reducing out-of-pocket costs (e.g., through RWHAP or ADAP cost-sharing assistance, manufacturer copayment-assistance programs, or by prescribing generic drugs instead of more costly brand-name products) has been associated with improved adherence.[50] 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 when decisions on ART are made. Asking people with HIV about their copays and working with case management specialists can help to identify and overcome this structural barrier to clinical care.

Medicaid maximum allowable copayments are statutorily capped at $4 for preferred drugs; in some states, maximum allowable copayments can increase to up to $8 for certain non-preferred drugs for beneficiaries with income <150% of the federal poverty level. For commercial insurers, cost sharing generally is subject to maximum payment rules under the ACA, which increase annually. 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 also may 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.

ADAPs make ARVs and other prescription drugs accessible to people with HIV who are underinsured and have limited financial resources, particularly during lapses in insurance coverage.[51,52] Furthermore, many ADAPs provide premium and/or cost-sharing assistance to eligible clients covered by Medicaid, commercial insurance plans, employer-sponsored insurance plans, or Medicare.[20] Nationally, ADAP utilization increased from 14% of all people with HIV in 2008 to 22% in 2021, with persistent disparities in coverage by race and sex.[53]

Medicare Beneficiaries With HIV

ARV cost considerations associated with Medicare coverage are increasingly important as more people with HIV age into Medicare. According to CDC HIV prevalence data, 15% of all people with

diagnosed HIV in the United States were aged 65 or older in 2022 (compared with 10% in 2019); an additional 27% were aged 55 to 64, with the vast majority expected to age into Medicare over the next 10 years.[54] Enrollment in Medicare can change out-of-pocket costs, which can cause unexpected changes to ART affordability and, ultimately, adherence.

Medicare Part D prescription drug cost sharing includes deductibles and copayments or coinsurance, including out-of-pocket payments of up to 25%. However, beginning in 2025, the Inflation Reduction Act (IRA) capped annual out-of-pocket drug spending in Medicare Part D at $2,000 ($2,100 in 2026; $2,400 in 2027)—a provision projected to benefit people with HIV more than beneficiaries managing most other chronic conditions, with estimated average savings of $3,181 annually and a 69% reduction in out-of-pocket spending.[55-57]

Medicare Part B cost sharing is not subject to out-of-pocket caps. Where provider-administered drugs—such as LA CAB/RPV, ibalizumab-uiyk (IBA) infusions, or subcutaneously (SQ) administered lenacapavir (LEN)—are covered under Medicare Part B, beneficiary cost sharing can be up to 20% of all medication costs.[58]

People with HIV who are low income and enrolled in Medicare may qualify for subsidies to defray Part D cost-sharing payments or the Qualified Medicare Beneficiary program to defray Part B cost-sharing payments. Medicare Advantage and Part D plans are now required to offer beneficiaries an option to enroll in a Medicare Prescription Payment Plan[59] authorized under the IRA, which will allow beneficiaries to pay cost sharing associated with high-cost prescription drugs in capped monthly payments instead of a single pharmacy payment. Manufacturer copay assistance programs may not be applied toward Medicare plan cost sharing, but assistance from state/territorial ADAPs, other State Pharmaceutical Assistance Programs, and independent foundations (e.g., Patient Access Network Foundation, Patient Advocate Foundation) may provide cost-sharing support if financial eligibility criteria are met.

In addition to its Medicare Part D cost-sharing provisions intended to lower out-of-pocket costs for beneficiaries, the IRA also requires the Secretary of the U.S. Department of Health and Human Services to negotiate prices with manufacturers for certain drugs with the highest total Part D and Part B spending. Ten Part D drugs were selected for price negotiation in 2026 (2026 pricing was finalized in 2024), with another 15 Part D drugs selected for 2027, 15 Part D and Part B drugs for 2028, and 20 Part D and Part B drugs selected for 2029 and thereafter. The selected drugs will come from the 50 with the highest total Medicare Part D spending and the 50 with the highest total Medicare Part B spending. Although ARV drugs did not qualify for negotiated pricing during the 2026 and 2027 cycles, Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) has been selected for negotiated pricing starting in 2028.[60]

Generic Antiretrovirals and Multi-tablet Regimens

In 2024, savings to the U.S. health care system generated from the use of generic drugs and biosimilar products totaled $467 billion, including $142 billion and $62.1 billion in savings to Medicare and Medicaid, respectively.[61] Total generic and biosimilar savings over the past 10 years are estimated at $3.4 trillion.

With substantial improvements in the long-term safety and effectiveness of contemporary ART, a number of regimens and regimen components recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) remain listed beyond their patent protection date and are or will be available as lower-cost generic options (see Initial Combination Antiretroviral Regimens for People With HIV). Keen interest exists in assessing the economic value of using newer, more expensive drugs compared with older, less expensive generic drugs that have

established clinical safety and efficacy, such as generic tenofovir disoproxil fumarate (TDF), which has been available since 2018.

A nationwide cross-sectional analysis of 2019 Medicare Part D formulary and pricing data investigated the cost-effectiveness of generic TDF-based regimens versus branded tenofovir alafenamide (TAF)–based regimens.[62] The study demonstrated that the similar efficacy—but slightly improved toxicity profile—of the TAF-based regimens would justify no more than a $1,000 higher annual premium for the TAF-based regimens than for generically available TDF-based regimens.

A cost-containment analysis evaluated the use of branded dolutegravir (DTG) plus generic lamivudine (3TC) as a two-pill regimen compared with a branded single-tablet regimen (STR).[63] Model findings supported that if 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; similarly, if 25% of people with sustained viral suppression switched to branded DTG plus generic 3TC maintenance therapy, the cost savings would exceed $3 billion in 5 years.[63]

Because all commercially available STRs listed among the *Recommended Initial Regimens for Most People With HIV* and *Initial Antiretroviral Regimens for Certain Clinical Scenarios* are branded products, including STRs that contain 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.

However, to the extent that pill burden, rather than drug frequency, results in reduced adherence, generic ART could lead to decreased costs but at the potential expense of worsening virologic suppression rates and poorer clinical outcomes.[45,46] An additional 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 remain limited, particularly based on virologic outcomes and especially following viral suppression. One large observational cohort study demonstrated a small but statistically significant virologic efficacy benefit associated with STRs.[63] In this study, the time to treatment discontinuation was shorter for non-STRs than for once-daily STR 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 with DTG plus ABC/3TC, both when used as an initial ARV regimen and when people with viral suppression on the STR were switched to the two-pill formulation as a cost-saving strategy.[64]

A 2025 budget impact analysis of Washington State Medicaid's elimination of prior authorization requirements for all ARVs illustrates the complex tradeoffs inherent in formulary management policy. Using actual net drug costs, including rebates, the analysis projected that the removal of prior authorizations favoring generic TDF-based multi-tablet regimens would increase Medicaid ARV expenditures by an estimated $109.9 million to $157.7 million over 5 years, driven primarily by a shift toward higher-cost branded single-tablet regimens.[65]

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 an

equivalent generic ARV product, the generic drug prescription paradoxically may result in higher out-of-pocket costs.

Antiretroviral Therapy Regimen Selection and Costs Borne by the Person With HIV

When limited health care coverage or out-of-pocket costs restrict access to a specific ART regimen, providers should work with people with HIV to identify a clinically appropriate and affordable alternative. Any decision to select or modify an ART regimen based on cost should be evaluated against the person's full ARV history, prior virologic responses, documented or suspected drug resistance, risk of adverse effects, and the potency and durability of the proposed alternative; cost considerations must never compromise virologic efficacy or long-term treatment outcomes **(AIII).**

For people who are uninsured or face significant cost sharing, "hybrid" regimens (e.g., a branded integrase strand transfer inhibitor [INSTI] or boosted protease inhibitor [PI] paired with a generic nucleoside reverse transcriptase inhibitor [NRTI] backbone) or fully generic multi-tablet regimens can substantially reduce monthly costs while remaining within the scope of a Guideline-recommended regimen. Pricing for generic components is typically lowest at direct-to-consumer pharmacies or clinic in-house pharmacies, particularly those participating in the 340B Drug Pricing Program. Sending a proposed regimen to the patient's pharmacy before finalizing it is the most reliable way to determine actual out-of-pocket cost.

Table 22a provides benchmark pricing across brand-specific, hybrid, and fully generic initial regimen options. People on ART who have no history of drug resistance or viral failure but require a change to their ART regimen can likely switch to a regimen recommended for initial ART (see Table 22a). Additionally, several regimens not used as initial therapy have been studied extensively as switch therapy; costs of these regimens are in Table 22b. Table 22c provides pricing for all individual and coformulated ARV medications, including generic medications that are not components of currently recommended regimens but retain demonstrated antiviral efficacy and may offer acceptable tolerability profiles. Prescribing regimen components that are not currently recommended may warrant consideration when cost is the predominant constraint on regimen selection or continuation and when their use can be supported by the person's treatment history and resistance profile.

Long-Acting Injectable Antiretroviral Therapy

Cabotegravir/rilpivirine (CAB/RPV), IBA, and LEN are parenteral ARVs with unique pharmacokinetic characteristics that allow for long-acting (LA) administration via intramuscular (IM) injection, intravenous (IV) infusion, and SQ injection, respectively. IBA and LEN are approved for use among people with HIV who are highly treatment experienced, typically in combination with an optimized background regimen that includes at least one daily oral ARV drug product and are associated with unique cost considerations. Conversely, monthly or bimonthly LA CAB/RPV injections can be prescribed and administered as a complete regimen replacement for daily oral ARV regimens.

Wholesale Acquisition Cost (WAC) prices for the LA CAB/RPV formulations are comparable to those of commonly prescribed oral regimens on an annual basis. However, LA HIV treatment options requiring administration by a licensed medical provider may be associated with costs not typically associated with oral ART, including clinic visit and administration fees, medical benefit determinations and prior authorization requirements, appointment scheduling and follow-up to ensure adherence, upfront medication purchasing costs incurred by clinics, and inadequate "buy-and-bill" insurance reimbursements.

Cost-effectiveness modeling indicates that long-acting ART may be particularly advantageous for people struggling with adherence to daily oral regimens.[66-68] Studies have demonstrated that long-acting ART can achieve similar or better clinical outcomes than oral ART, particularly when adherence is factored into the equation. In cost terms, LA CAB/RPV may lead to lifetime savings, given lower health care expenditures associated with improved viral suppression and reduced risk of HIV transmission.

Costs and Cost-Effectiveness of Antiretroviral Regimens for Highly Treatment-Experienced People With Multidrug-Resistant HIV

For people with multidrug-resistant (MDR) HIV, an ARV regimen that includes IV IBA, SQ LEN, or oral fostemsavir can be effective in achieving viral suppression, though costly. 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.[69,70]

340B Drug Pricing Program, Prescription Drug Affordability, and Program Savings for People With HIV

Created by Congress in 1992, the 340B Drug Discount Program requires pharmaceutical manufacturers to sell drugs at a discount to certain hospitals and federally funded clinics providing safety net care, including RWHAP providers and state/territorial ADAPs. 340B discounts help to ensure the affordability of outpatient prescription drugs for people with HIV who are uninsured and underinsured and to retain any revenue associated with discounted sales. This revenue, or program savings, is generated when 340B-covered entities are able to purchase discounted drugs but are reimbursed by third-party payers at usual and customary rates that do not account for discounted purchases. Although potentially incentivizing providers to prescribe higher-cost brand-name drugs that yield substantially greater revenue than generic alternatives, 340B savings can be used to "stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services."[71]

By purchasing ARV drugs and other essential medicines at significantly reduced prices, covered entities can reinvest savings into essential HIV care and support services, including case management, behavioral health care, offsetting uncompensated care, transportation, adherence support, and outreach efforts. These services can help improve engagement in HIV care, medication adherence, and viral suppression rates.[20]

Costs and Cost-Effectiveness of Routine Laboratory Services for People With HIV on Antiretroviral Therapy

Several studies have examined the value of laboratory services in HIV care. One analysis suggested that there may be no clinical benefit to continuing CD4 monitoring in people with suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[72] In the United States, one modeling study found that reducing biannual CD4 monitoring to annual monitoring could save approximately $10 million per year.[73] Another study reviewed the records of 429 hospitalizations for 274 people with HIV during a 6-month period. The inpatient chart review demonstrated that 45% of ordered laboratory tests were not indicated. During this 6-month period at this single site, the estimated cost of excess and inappropriate laboratory testing totaled $14,000 to $92,000.[74]

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 Panel's recommendation to perform resistance testing before ART initiation and at the time of virologic failure.[75,76] More recent cost-effectiveness analyses have revisited the value of baseline, pre-treatment genotype testing in the setting of INSTI plus two NRTI regimens. One modeling study suggested that INSTI-specific genotype testing before initiation of a DTG plus two-NRTI regimen is 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.[77] A second modeling study found that standard (NRTI, non-nucleoside reverse transcriptase inhibitor, PI) genotype testing before ART initiation also is not cost-effective because it may have little impact on outcomes, given the use of an INSTI plus two NRTIs in first-line treatment.[78] Both modeling studies assessed the use of genotype testing only for decision-making for initial ART and presumed that genotype 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 an INSTI plus two-NRTI regimen. 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 oral (TDF or TAF) plus (3TC or FTC) or IM cabotegravir (CAB) as pre-exposure prophylaxis (PrEP), which are 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 or an INSTI-based regimen for post-exposure prophylaxis (see Drug-Resistance Testing).

Costs and Cost-Effectiveness of Comprehensive HIV Care

Comprehensive person-centered HIV care offers substantial clinical benefits.[79] Such programs include the 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, 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.[80-82]

RWHAP provides a critical source of outpatient HIV clinical care for people with HIV who have low incomes and remain uninsured or underinsured under the ACA or who require wraparound support.[38] 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.[28] RWHAP funds can be used to provide eligible individuals with services related to the delivery of HIV care, the treatment of related conditions, and support, as well as to address identified barriers to care. However, RWHAP funds cannot be used for inpatient care and services.[83]

A 2025 simulation study using a validated compartmental HIV transmission model calibrated to data from 31 U.S. cities provides additional evidence of RWHAP's public health value and cost implications. The study projected that eliminating RWHAP services could result in an estimated 75,436 additional HIV infections (95% credible interval: 19,251 to 134,175) through 2030—a 49% increase over projected baseline incidence. RWHAP interruptions of 18 and 42 months were projected to yield 19% and 38% more people with HIV, respectively, with substantial variation across cities (ranging from a 9% increase in Riverside, California, to a 110% increase in Baltimore, Maryland).[84] Given the substantial lifetime treatment costs associated with HIV, these projections

highlight the fiscal as well as clinical value of maintaining comprehensive, uninterrupted HIV care through programs such as RWHAP.

Comprehensive HIV care and treatment often requires 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 people's ability 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. Providers should, therefore, remain informed of current insurance and payment structures, ART costs (see Tables 22a, 22b, and 22c 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 pharmacists, social workers, case managers, financial service providers, and peer navigators to understand the medication benefits and any potential financial hurdles to prescription fulfillment and full adherence. This information will help providers identify treatment options that are safe, effective, and affordable. Engaging people with HIV in discussions about cost constraints during regimen selection will likely facilitate adherence. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAPs 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 21. 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 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, though caps on out-of-pocket spending for drugs covered by Medicare Part D went into effect in 2025; 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 21. 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, U.S. Department of Defense, U.S. Public Health Service (including the Indian Health Service), and U.S. Coast Guard. The FCP of a drug includes a 24% discount on a drug's average price paid by nonfederal purchasers. Additional discounts may be applied if nonfederal purchase prices increase faster than the CPI-U inflation rate. Big Four prices may be 40% to 50% below list prices. Veterans Affairs 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.
Jails and Prisons	Under the U.S. Constitution, correctional facilities have a legal obligation to provide necessary medical care, including prescription drugs, to incarcerated individuals.[a] Jails and prisons generally do not have access to discounted drugs available to government programs, such as Medicaid or "Big Four" purchasers (see Veterans Affairs above), but may benefit from centralized municipal or state purchasing mechanisms. Jails and prisons also may be able to purchase discounted ARV drugs and other medications under the 340B Drug Pricing Program, either as a recipient of certain federal funds associated with STI, HIV, and viral hepatitis prevention, or in partnership with other 340B-covered entities contracted to provide health care services to jailed or incarcerated individuals (e.g., disproportionate share hospital programs, community health centers). Since 2023, states are expected to suspend (not terminate) Medicaid coverage during incarceration and must collaborate with correctional facilities to assist incarcerated individuals who are not currently enrolled in Medicaid with submitting applications during incarceration using presumptive eligibility. Minimum benefits expected by CMS in state waiver proposals include case management services for pre- and post-release (including linkage to outpatient HIV care), medication-assisted therapy for substance use disorders, and at least a 30-day supply of medications at release.

Table 21. Insurance and Health Program Prescription Drug Pricing and Access

Insurance/Health Program	Prescription Drug Pricing and Access
	RWHAP programs and ADAPs also may provide time-limited HIV care and prescription drug access support for people with HIV in local prisons and jails.
Manufacturer and Charitable Prescription Drug Assistance Programs	Manufacturer PAPs are run by, or in association with, pharmaceutical companies to provide free or low-cost medications to people who meet certain eligibility requirements, including FPL-based income limits. A CAP is operated by manufacturers to provide assistance with cost-sharing requirements (including deductibles, copayments, and coinsurance) associated with prescription drug fills/refills for individuals with private health insurance. Pharmaceutical company CAPs cannot be used by individuals covered by Medicaid, Medicare, or other state and federal programs. Charitable third-party assistance programs, such as Patient Advocate Foundation Co-pay Relief, provide cost-sharing assistance to people who meet financial eligibility requirements. NASTAD maintains a number of PAP and CAP resources for use in clinical practice.

[a] *Estelle v. Gamble*[85]

Key: ACA = Affordable Care Act; ADAP = AIDS Drug Assistance Program; AMP = average manufacturer price; ARV = antiretroviral; ASP = average sales price; CAP = cost-sharing assistance program; CMS = Centers for Medicare & Medicaid Services; CPI-U = consumer price index-urban; FCP = federal ceiling price; FPL = federal poverty level; MDRP= Medicaid Drug Rebate Program; NASTAD = National Alliance of State & Territorial AIDS Directors; PAP = patient assistance program; PBM = pharmacy benefits manager; RWHAP = Ryan White HIV/AIDS Program; STI = sexually transmitted infection

Table 22a. Benchmark Prices for Recommended Initial Antiretroviral Therapy Regimens

Cash-pay estimate applicability: These estimates approximate out-of-pocket cost for individuals paying cash for antiretroviral therapy (ART) in narrowly defined circumstances—those who are uninsured, underinsured, or otherwise ineligible for the Ryan White HIV/AIDS Program, AIDS Drug Assistance Program, or manufacturer patient assistance programs. They do **not** reflect cost-sharing obligations (copayments, coinsurance, deductibles) where primary health coverage applies to these products. Generic-component estimates reflect direct-to-consumer pharmacy pricing (e.g., Cost Plus Drugs); Wholesale Acquisition Cost (WAC) is used as the acquisition-cost surrogate for branded products without National Average Drug Acquisition Cost (NADAC) data. For hybrid regimens, the WAC and AWP columns reflect the branded component(s) only. The generic component(s) are priced via NADAC in the NADAC column. The Estimated Cash-Pay Cost is the sum of branded WAC + generic NADAC.

Note: All prices are approximate monthly costs based on standard dosing quantities. Prices may vary by pharmacy, geographic region, and patient assistance program eligibility.

Regimen	Evidence Rating[a]	Specific Option	Option Type[b]	WAC	AWP	NADAC	Est. Cash-Pay Cost[c]
Table 6a—Recommended Initial Regimens for Most People With HIV							
BIC/TAF/FTC	**AI**	Biktarvy (bictegravir 50 mg/ tenofovir alafenamide 25 mg/ emtricitabine 200 mg)	Brand-Only	$4,216	$5,059	See WAC	$4,216
DTG + TAF/FTC	**AI**	Tivicay (dolutegravir 50 mg) + Descovy (tenofovir alafenamide 25 mg/emtricitabine 200 mg)	Brand-Only	$4,597	$5,517	See WAC	$4,597
DTG + TDF/FTC	**AI**	Tivicay (dolutegravir 50 mg) + Truvada (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Brand-Only	$2,395 (DTG) + $1,842 (TDF/FTC)	$2,874 (DTG) + $2,211 (TDF/FTC)	See WAC	$4,237
DTG + TDF/FTC	**AI**	Tivicay (dolutegravir 50 mg) + Generic tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Hybrid	$2,395 (DTG)	$2,874 (DTG)	$14 (TDF/FTC)	$2,409
DTG/3TC	**AI**	Dovato (dolutegravir 50 mg/ lamivudine 300 mg)	Brand-Only	$3,250	$3,901	See WAC	$3,250

Table 22a. Benchmark Prices for Recommended Initial Antiretroviral Therapy Regimens

Regimen	Evidence Rating[a]	Specific Option	Option Type[b]	WAC	AWP	NADAC	Est. Cash-Pay Cost[c]
DTG + 3TC	**AI**	Tivicay (dolutegravir 50 mg) + Generic lamivudine 300 mg	Hybrid	$2,395 (DTG)	$2,874 (DTG)	$39 (3TC)	$2,434
Table 6a—For People With History of CAB-LA Use as PrEP (INSTI Genotype Testing Recommended)							
DRV/c/TAF/FTC	**AIII**	Symtuza (darunavir 800 mg/ cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg)	Brand-Only	$4,717	$5,660	See WAC	$4,717
DRV/c + TAF/FTC	**AIII**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Descovy (tenofovir alafenamide 25 mg/ emtricitabine 200 mg)	Brand-Only	$4,669	$5,603	See WAC	$4,669
DRV/c + TDF/FTC	**AIII**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Truvada (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Brand-Only	$2,467 (DRV/c) + $1,842 (TDF/FTC)	$2,960 (DRV/c) + $1,842 (TDF/FTC)	See WAC	$4,309
DRV/c + TDF/FTC	**AIII**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Generic tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	Hybrid	$2,467 (DRV/c)	$2,960 (DRV/c)	$14 (TDF/FTC)	$2,481
DRV + r + TDF/FTC	**AIII**	Prezista (darunavir 800 mg) + Norvir (ritonavir 100 mg) + Truvada (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Brand-Only	$2,158 (DRV) + $257 (r) + $1,842 (TDF/FTC)	$2,590 (DRV) + $309 (r) + $2,643 (TDF/FTC)	See WAC	$4,257
DRV + r + TDF/FTC	**AIII**	Generic darunavir 800 mg + Generic ritonavir 100 mg + Generic tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	Generic	N/A	N/A	$64 (DRV) + $20 (r) + $14 (TDF/FTC)	$98

Table 22a. Benchmark Prices for Recommended Initial Antiretroviral Therapy Regimens

Regimen	Evidence Rating[a]	Specific Option	Option Type[b]	WAC	AWP	NADAC	Est. Cash-Pay Cost[c]
Table 6b—Initial Regimens for Certain Clinical Scenarios							
INSTI Plus Two NRTIs							
DTG/ABC/3TC	**AII**	Triumeq (dolutegravir 50 mg/ abacavir 600 mg/lamivudine 300 mg)	Brand-Only	$4,014	$4,817	See WAC	$4,014
DTG + ABC/3TC	**AII**	Tivicay (dolutegravir 50 mg) + Generic abacavir 600 mg/ lamivudine 300 mg	Hybrid	$2,395 (DTG)	$2,874 (DTG)	$42 (ABC/3TC)	$2,437
Boosted PI Plus Two NRTIs							
DRV/c/TAF/FTC	**BI**	Symtuza (darunavir 800 mg/ cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg)	Brand-Only	$4,717	$5,660	See WAC	$4,717
DRV/c + TAF/FTC	**BI**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Descovy (tenofovir alafenamide 25 mg/ emtricitabine 200 mg)	Brand-Only	$4,669	$5,603	See WAC	$4,669
DRV/c + TDF/FTC	**BI**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Truvada (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Brand-Only	$2,467 (DRV/c) + $1,842 (TDF/FTC)	$2,960 (DRV/c) + $1,842 (TDF/FTC)	See WAC	$4,309
DRV/c + TDF/FTC	**BI**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Generic tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	Hybrid	$2,467 (DRV/c)	$2,960 (DRV/c)	$14 (TDF/FTC)	$2,481
DRV + r + TDF/FTC	**BI**	Prezista (darunavir 800 mg) + Norvir (ritonavir 100 mg) + Truvada (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Brand-Only	$2,158 (DRV) + $257 (r) + $1,842 (TDF/FTC)	$2,590 (DRV) + $309 (r) + $2,643 (TDF/FTC)	See WAC	$4,257

Table 22a. Benchmark Prices for Recommended Initial Antiretroviral Therapy Regimens

Regimen	Evidence Rating[a]	Specific Option	Option Type[b]	WAC	AWP	NADAC	Est. Cash-Pay Cost[c]
DRV + r + TDF/FTC	**BI**	Generic darunavir 800 mg + Generic ritonavir 100 mg + Generic tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	Generic	N/A	N/A	$64 (DRV) + $20 (r) + $14 (TDF/FTC)	$98
DRV/c + ABC/3TC	**BII**	Prezcobix (darunavir 800 mg/ cobicistat 150 mg) + Generic abacavir 600 mg/lamivudine 300 mg	Hybrid	$2,467 (DRV/c)	$2,960 (DRV/c)	$42 (ABC/3TC)	$2,509
DRV + r + ABC/3TC	**BII**	Generic darunavir 800 mg + Generic ritonavir 100 mg + Generic abacavir 600 mg/lamivudine 300 mg	Generic	N/A	N/A	$64 (DRV) + $20 (r) + $42 (ABC/3TC)	$126
NNRTI Plus Two NRTIs							
DOR/TDF/3TC	**BI**	Delstrigo (doravirine 100 mg/ tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg)	Brand-Only	$2,870	$3,444	See WAC	$2,870
DOR + TAF/FTC	**BIII**	Pifeltro (doravirine 100 mg) + Descovy (tenofovir alafenamide 25 mg/emtricitabine 200 mg)	Brand-Only	$4,084	$4,901	See WAC	$4,084
DOR + TDF/FTC	**BIII**	Pifeltro (doravirine 100 mg) + Truvada (tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg)	Brand-Only	$1,882 (DOR) + $1,842 (TDF/FTC)	$2,258 (DOR) + $2,642 (TDF/FTC)	See WAC	$3,724
DOR + TDF/FTC	**BIII**	Pifeltro (doravirine 100 mg) + Generic tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	Hybrid	$1,882 (DOR)	$2,258 (DOR)	$14 (TDF/FTC)	$1,896
RPV/TAF/FTC	**BII**	Odefsey (rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg)	Brand-Only	$4,025	$4,830	See WAC	$4,025

Notes: WAC and AWP data are as of May 2026.[86] NADAC data are from the CMS National Average Drug Acquisition Cost survey,[87] effective date May 27, 2026.

[a] Evidence ratings correspond to those recommended for initial therapy in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV (see Initial Combination Antiretroviral Regimens for People With HIV).

Table 22a. Benchmark Prices for Recommended Initial Antiretroviral Therapy Regimens

[b] Option types: Brand-Only = all branded components; Hybrid = mix of branded and generic components; Generic = all components available as generics.

[c] Estimated Cash-Pay Cost reflects the sum of NADAC (for generic components) and WAC (for branded components) as a practical floor estimate for uninsured patients using retail or DTC pharmacies.

Key: 3TC = lamivudine; ABC = abacavir; AWP = Average Wholesale Price; BIC = bictegravir; CAB-LA = long-acting cabotegravir; CMS = Centers for Medicare & Medicaid Services; DOR = doravirine; DRV/c = darunavir/cobicistat; DTG = dolutegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; N/A = not applicable; NADAC = National Average Drug Acquisition Cost; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PrEP = pre-exposure prophylaxis; r = ritonavir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; WAC = Wholesale Acquisition Cost

Table 22b. Benchmark Prices for Switch and Optimization Antiretroviral Therapy Regimens in the Setting of Viral Suppression

For people who have no history of resistance or virologic failure, one can likely switch to a regimen recommended for initial antiretroviral therapy (ART) (see Table 22a). Additionally, several regimens not used as initial therapy have been studied extensively as switch therapy. The cost data for these regimens are listed below.

CASH-PAY ESTIMATE APPLICABILITY: These estimates approximate out-of-pocket cost for individuals paying cash for ART in narrowly defined circumstances—those who are uninsured, underinsured, or otherwise ineligible for the Ryan White HIV/AIDS Program, AIDS Drug Assistance Program, or manufacturer patient assistance programs. They **do not** reflect cost-sharing obligations (copayments, coinsurance, deductibles) where primary health coverage applies to these products. Generic-component estimates reflect direct-to-consumer pharmacy pricing (e.g., Cost Plus Drugs); Wholesale Acquisition Cost (WAC) is used as the acquisition-cost surrogate for branded products without National Average Drug Acquisition Cost (NADAC) data. For hybrid regimens, the WAC and AWP columns reflect the branded component(s) only. The generic component(s) are priced via NADAC in the NADAC column. The Estimated Cash-Pay Cost is the sum of branded WAC + generic NADAC.

Note: In Table 22b, WAC, AWP, NADAC, and the Estimated Cash-Pay Cost are **monthly values unless otherwise noted.**

Regimen	Specific Option	Option Type[a]	WAC	AWP	NADAC	Est. Cash-Pay Cost[b]
Two-Drug Oral Regimens						
Two-Drug Regimens—INSTI + NNRTI						
DTG/RPV	Juluca (dolutegravir 50 mg/rilpivirine 25 mg)	Brand-Only	$3,762	$4,515	See WAC	$3,762
Two-Drug Regimens—NNRTI + NRTI						
DOR/ISL	Idvynso (doravirine 100 mg/islatravir 0.25 mg)	Brand-Only	$4,455	$5,346	See WAC	$4,455
Two-Drug Regimens—Boosted Protease Inhibitor + Lamivudine						
DRV/c + 3TC	Prezcobix (darunavir 800 mg/cobicistat 150 mg) + Epivir (lamivudine 300 mg)	Brand-Only	$2,467 (DRV/c) + $416 (3TC)	$2,960 (DRV/c) + $499 (3TC)	See WAC	$2,883
DRV/c + 3TC	Prezcobix (darunavir 800 mg/cobicistat 150 mg) + Generic lamivudine 300 mg	Hybrid	$2,467 (DRV/c)	$2,960 (DRV/c)	$39 (3TC)	$2,506

Table 22b. Benchmark Prices for Switch and Optimization Antiretroviral Therapy Regimens in the Setting of Viral Suppression

Regimen	Specific Option	Option Type[a]	WAC	AWP	NADAC	Est. Cash-Pay Cost[b]
DRV + r + 3TC	Prezista (darunavir 800 mg) + Norvir (ritonavir 100 mg) + Epivir (lamivudine 300 mg)	Brand-Only	$2,158 (DRV) + $257 (r) + $416 (3TC)	$2,590 (DRV) + $309 (r) + $499 (3TC)	See WAC	$2,831
DRV + r + 3TC	Generic darunavir 800 mg + Generic ritonavir 100 mg + Generic lamivudine 300 mg	Generic	N/A	N/A	$64 (DRV) + $20 (r) + $39 (3TC)	$123
Two-Drug Regimen—Boosted Darunavir + Dolutegravir						
DRV + r + DTG	Tivicay (dolutegravir 50 mg) + Prezista (darunavir 800 mg) + Norvir (ritonavir 100 mg)	Brand-Only	$2,395 (DTG) + $2,158 (DRV) + $257 (r)	$2,874 (DTG) + $2,590 (DRV) + $309 (r)	See WAC	$4,810
DRV + r + DTG	Tivicay (dolutegravir 50 mg) + Generic darunavir 800 mg + Generic ritonavir 100 mg	Hybrid	$2,395 (DTG)	$2,874 (DTG)	$64 (DRV) + $20 (r)	$2,479
Long-Acting Intramuscular Cabotegravir/Rilpivirine						
CAB/RPV (Every 4 Weeks)	Cabenuva (cabotegravir 400 mg/2 mL + rilpivirine 600 mg/2 mL); 1 IM injection set every 4 weeks	Brand-Only	$4,639 (every 4 weeks)	$5,706 (every 4 weeks)	See WAC	$4,639
CAB/RPV (Every 8 Weeks)	Cabenuva (cabotegravir 600 mg/3 mL + rilpivirine 900 mg/3 mL); 1 IM injection set every 8 weeks	Brand-Only	$6,959 (every 8 weeks)	$8,560 (every 8 weeks)	See WAC	$6,959

Notes: Cross-references: For pricing of individual ARV components, see Table 22c. For initial-therapy benchmark pricing, see Table 22a.

WAC and AWP data are as of May 2026.[86] NADAC data are from the CMS National Average Drug Acquisition Cost survey,[87] effective date May 27, 2026.

[a] Option types: Brand-Only = all branded components; Hybrid = mix of branded and generic components; Generic = all components available as generics.

[b] Estimated Cash-Pay Cost reflects the sum of NADAC (for generic components) and WAC (for branded components) as a practical floor estimate for uninsured patients using retail or DTC pharmacies.

Table 22b. Benchmark Prices for Switch and Optimization Antiretroviral Therapy Regimens in the Setting of Viral Suppression

Key: 3TC = lamivudine; ARV = antiretroviral; AWP = Average Wholesale Price; CAB = cabotegravir; CMS = Centers for Medicare & Medicaid Services; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; IM = intramuscular; ISL = islatravir; INSTI = integrase strand transfer inhibitor; N/A = not applicable; NADAC = National Average Drug Acquisition Cost; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; r = ritonavir; WAC = Wholesale Acquisition Cost

Table 22c. Benchmark Prices for Individual Antiretroviral Medications

Table 22c provides benchmark pricing for antiretroviral (ARV) products across drug classes—including individual agents and coformulated products—and is intended as a comprehensive pricing reference. Organized by drug class rather than by clinical indication, it complements Tables 22a and 22b by enabling clinicians to look up the cost of specific ARV products when evaluating individual component substitutions, comparing coformulated options, or assessing costs outside the regimen-level comparisons provided in those tables. Agents no longer recommended by the Panel due to serious adverse effects are not included in this table (see footnote).

Note: In Table 22c, WAC, AWP, and NADAC are **monthly values unless otherwise noted.**

ARV Drug *Brand and Generic Names*	**Strength, Formulation**	**Quantity**	**WAC**	**AWP**	**NADAC[a]**
NRTIs					
Abacavir *Generic Only*	300-mg tablet	60 tablets	$100–$150	$578–$603	$38
Emtricitabine *Generic or Emtriva*	200-mg capsule	30 capsules	Generic $390–$536/ Emtriva $537	Generic $482–$644/ Emtriva $644	$372[b]
Lamivudine *Generic or Epivir*	300-mg tablet	30 tablets	Generic $40–$415/ Epivir $416	Generic $429/ Epivir $499	$39
Tenofovir Disoproxil Fumarate *Generic or Viread*	300-mg tablet	30 tablets	Generic $27–$300/ Viread $1,254	Generic $167–$1,216/ Viread $1,504	$10
NRTI Combination Products					
Abacavir/Lamivudine *Generic Only*	600-mg/300-mg tablet	30 tablets	$100–$302	$1,393–$1,395	$42
Tenofovir Alafenamide/Emtricitabine *Descovy*	25-mg/200-mg tablet	30 tablets	$2,202	$2,643	See WAC
Tenofovir Disoproxil Fumarate/Emtricitabine *Generic or Truvada*	300-mg/200-mg tablet	30 tablets	Generic $25–$853/ Truvada $1,842	Generic $70–$2,100/ Truvada $2,211	$14

Table 22c. Benchmark Prices for Individual Antiretroviral Medications

ARV Drug *Brand and Generic Names*	Strength, Formulation	Quantity	WAC	AWP	NADAC[a]
Tenofovir Disoproxil Fumarate/Lamivudine *Cimduo*	300-mg/300-mg tablet	30 tablets	$1,244	$1,493	See WAC
NNRTIs					
Doravirine *Pifeltro*	100-mg tablet	30 tablets	$1,882	$2,258	See WAC
Efavirenz *Generic*	600-mg tablet	30 tablets	$80–$894	$1,043–$1,118	$42
Etravirine *Generic or Intelence*	200-mg tablet	60 tablets	Generic $1,287/ Intelence $1,498	Generic $1,609/ Intelence $1,797	$677
Rilpivirine *Generic or Edurant*	25-mg tablet	30 tablets	Generic $1,254/ Edurant $1,483	Generic $1,505/ Edurant $1,780	See WAC
PIs					
Atazanavir *Generic or Reyataz*	200-mg capsule	60 capsules	Generic $178–$316/ Reyataz $1,463	Generic $1,502–$1,668/Reyataz $1,756	$63
Atazanavir *Generic or Reyataz*	300-mg capsule	30 capsules	Generic $178–$316/ Reyataz $1,449	Generic $1,502–$1,652/Reyataz $1,739	$81
Atazanavir/Cobicistat *Evotaz*	300-mg/150-mg tablet	30 tablets	$1,605	$1,927	See WAC
Darunavir *Generic or Prezista*	600-mg tablet	60 tablets	Generic $60–$1,145/ Prezista $2,158	Generic $1,373–$2,388/Prezista $2,590	$69
Darunavir *Generic or Prezista*	800-mg tablet	30 tablets	Generic $60–$1,153/ Prezista $2,158	Generic $1,384–$2,388/Prezista $2,590	$64

Table 22c. Benchmark Prices for Individual Antiretroviral Medications

ARV Drug *Brand and Generic Names*	Strength, Formulation	Quantity	WAC	AWP	NADAC[a]
Darunavir/Cobicistat *Prezcobix*	800-mg/150-mg tablet	30 tablets	$2,467	$2,960	See WAC
Lopinavir/Ritonavir *Generic, or Kaletra*	200-mg/50-mg tablet	120 tablets	Generic $885/ Kaletra $1,024	Generic $1,106/ Kaletra $1,229	$525
Tipranavir *Aptivus*	250-mg capsule	120 capsules	$2,054	$2,466	See WAC
INSTIs (Integrase Strand Transfer Inhibitors)					
Dolutegravir *Tivicay*	50-mg tablet	30 tablets (or 60 tablets)	30 tablets $2,395/ 60 tablets $4,790	30 tablets $2,874/ 60 tablets $5,748	See WAC
Raltegravir *Isentress*	400-mg tablet	60 tablets	$2,131	$2,557	See WAC
Raltegravir *Isentress HD*	600-mg tablet	60 tablets	$2,131	$2,557	See WAC
Capsid Inhibitor					
Lenacapavir *Sunlenca*	300-mg tablet, or 927-mg/1.5-mL injection kit	4–5 tablets oral (1-time loading dose) then 1 injection kit (every 6 months)	4 tablets $3,250/ 5 tablets $4,184 (1-time loading dose) Injection kit $19,500 (every 6 months)	4 tablets $3,900/ 5 tablets $5,021 (1-time loading dose) Injection kit $23,400 (every 6 months)	See WAC
CCR5 Antagonist					
Maraviroc *Generic or Selzentry*	150-mg tablet	60 tablets	Generic $700/ Selzentry $1,730	Generic $1,764/ Selzentry $2,076	$549
Maraviroc *Generic or Selzentry*	300-mg tablet	60 tablets	Generic $700/ Selzentry $1,730	Generic $1,764/ Selzentry $2,076	$480

Table 22c. Benchmark Prices for Individual Antiretroviral Medications

ARV Drug *Brand and Generic Names*	Strength, Formulation	Quantity	WAC	AWP	NADAC[a]
CD4-Directed Post-Attachment Inhibitor					
Ibalizumab-uiyk *Trogarzo*	200-mg/mL vial	8 vials per month	$12,196	$14,635	See WAC
gp120-Directed Attachment Inhibitor					
Fostemsavir *Rukobia*	600-mg tablet	60 tablets	$9,651	$11,582	See WAC
Coformulated Complete Regimens—STRs					
Bictegravir/Tenofovir Alafenamide/Emtricitabine *Biktarvy*	50-mg/25-mg/ 200-mg tablet	30 tablets	$4,216	$5,059	See WAC
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine *Symtuza*	800-mg/150-mg/ 10-mg/200-mg tablet	30 tablets	$4,717	$5,660	See WAC
Dolutegravir/Abacavir/Lamivudine *Triumeq*	50-mg/600-mg/ 300-mg tablet	30 tablets	$4,014	$4,817	See WAC
Dolutegravir/Lamivudine *Dovato*	50-mg/300-mg tablet	30 tablets	$3,250	$3,901	See WAC
Dolutegravir/Rilpivirine *Juluca*	50-mg/25-mg tablet	30 tablets	$3,762	$4,515	See WAC
Doravirine/Islatravir *Idvynso*	100-mg/0.25-mg tablet	30 tablets	$4,455	$5,346	See WAC
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine *Delstrigo*	100-mg/300-mg/ 300-mg tablet	30 tablets	$2,870	$3,444	See WAC
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine *Generic Only*	600-mg/300-mg/ 200-mg tablet	30 tablets	$82–$252	$302–$3,414	$36

Table 22c. Benchmark Prices for Individual Antiretroviral Medications

ARV Drug *Brand and Generic Names*	Strength, Formulation	Quantity	WAC	AWP	NADAC[a]
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine *Symfi (Generic)*	600-mg/300-mg/ 150-mg tablet	30 tablets	$2,023	$2,427	See WAC
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine *Genvoya*	150-mg/150-mg/ 10-mg/200-mg tablet	30 tablets	$4,423	$5,307	See WAC
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine *Stribild*	150-mg/150-mg/ 300-mg/200-mg tablet	30 tablets	$4,639	$5,567	See WAC
Rilpivirine/Tenofovir Alafenamide/Emtricitabine *Odefsey*	25-mg/25-mg/ 200-mg tablet	30 tablets	$4,025	$4,830	See WAC
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine *Generic or Complera*	25-mg/300-mg/ 200-mg tablet	30 tablets	Generic $3,499/ Complera $4,025	Generic $4,374/ Complera $4,830	$3,450[b]
Copackaged Combination Products—Long-Acting Injectable Regimens					
Cabotegravir/Rilpivirine *Cabenuva*	**Every 4 Weeks:** • 400-mg/2-mL + 600-mg/2-mL vials	2 vials	$4,639 (every 4 weeks)	$5,706 (every 4 weeks)	See WAC
Cabotegravir/Rilpivirine *Cabenuva*	**Every 8 Weeks:** • 600-mg/2-mL + 900-mg/3-mL vials	2 vials (every 8 weeks)	$6,959 (every 8 weeks)	$8,560 (every 8 weeks)	See WAC
PK Enhancers (Boosters)					
Ritonavir *Generic or Norvir*	100-mg tablet	30 tablets	Generic $80–$160/ Norvir $257	Generic $278/ Norvir $309	$20

Notes: NADAC monthly costs are calculated as: average NADAC per unit × standard monthly dispensing quantity. NADAC per unit values reflect the average across all manufacturers with reported data.

WAC and AWP data are as of May 2026.[86] NADAC data are from the CMS National Average Drug Acquisition Cost survey,[87] effective date May 27, 2026.

Table 22c. Benchmark Prices for Individual Antiretroviral Medications

Certain older ARV medications, such as nevirapine and oral zidovudine, can cause serious adverse effects and are no longer recommended by the Panel for use in adults or adolescents and are not suitable for optimizing ARV in the setting of viral suppression; therefore, they are not included in this table.

[a] NADAC Note: For generic medications, NADAC reflects average pharmacy acquisition cost and provides the most relevant benchmark for cash-pay pricing at retail and DTC pharmacies. “See WAC” indicates NADAC data are unavailable.

[b] NADAC value appears anomalous (unexpectedly high or inconsistent with WAC). This may reflect authorized generic pricing, limited dispensing volume, or data entry issues in the CMS survey. Clinicians and patients should verify current pricing directly with the dispensing pharmacy.

Key: ARV = antiretroviral; AWP = Average Wholesale Price; CCR5 = C-C chemokine receptor type 5; CD4 = CD4 T lymphocyte; CMS = Centers for Medicare & Medicaid Services; DTC = direct-to-consumer; gp120 = glycoprotein 120; INSTI = integrase strand transfer inhibitor; NADAC = National Average Drug Acquisition Cost; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; STR = single-tablet regimen; WAC = Wholesale Acquisition Cost

Knowledge Gaps

Research is needed to—

- Examine how federal and state policies, insurance requirements and utilization management, and ART prices, affect people with HIV (including access, adherence, equity, and clinical outcomes) and Ending the HIV Epidemic in the U.S. initiative metrics and indicators.
- Examine the clinical impact of utilization management requirements—such as prior authorization and step therapy protocols—on ART adherence, virologic suppression, and treatment outcomes across diverse coverage settings and populations, including those experiencing coverage instability or care transitions.
- Investigate how insurance lapses and other transitions of care—including adolescents transitioning from pediatric to adult care, interstate relocation, and changes in employment—affect ART continuity, virologic suppression, and engagement in care among people with HIV.
- Understand the health care–associated and societal resource utilization of people with HIV who are not engaged in care, as well as the associated costs.
- Investigate how multimorbidity, aging, and polypharmacy affect ART selection and use for people with HIV, including access, equity, clinical outcomes, and patient- and health payer costs.
- Understand how accessible and widely used pharmacy-assisted programs are and the potential gaps for people who are uninsured.
- Examine the cumulative financial burden that can occur with additional medications to manage ART-associated side effects.
- Understand the implementation barriers and costs for people with HIV to access newer ART regimens (e.g., long-acting formulations) to improve equity and access.

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DRUG–DRUG INTERACTIONS

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Pharmacokinetic (PK) drug–drug interactions (DDIs) between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. When prescribing or switching drugs in an ARV regimen, clinicians should consider the potential for DDIs—both those affecting ARVs and those affecting concomitant medications. In some instances, changes in drug exposure may increase the frequency and/or severity of toxicities or affect therapeutic responses, risking treatment failure and/or resistance. Pharmacodynamic interactions can also lead to increased toxicity when medications that have overlapping adverse effects are coadministered.

Recommendations for managing a specific drug interaction may differ depending on whether a new ARV is being initiated in a person on a stable concomitant medication or a new concomitant medication is being initiated in a person on a stable ARV regimen. Furthermore, the magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways and drug transporter systems are prescribed together. When it is necessary to prescribe interacting medications, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions.

Drug–Drug Interaction Resources

Previous iterations of these guidelines contained extensive ARV DDI tables (last updated in September 2024). These tables remain available in the Archived Guidelines.

To screen for DDIs and review recommendations for dose modifications and monitoring of ARVs or concomitant medications, clinicians may use interactive web-based resources, such as the Liverpool HIV Drug Interaction Checker.

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:

- **Changes in gastric pH:** Acid-reducing agents, such as proton pump inhibitors, histamine 2 (or H2) antagonists, or antacids can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir, rilpivirine [RPV]).[1,2]
- **Binding of ARV drugs:** 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 medications.[3,4]

- **Effects on metabolic enzymes or transporters:** Drugs that induce or inhibit the enzyme cytochrome P450 (CYP), predominantly 3A4, or the efflux transporter P-glycoprotein in the intestines may reduce or promote the oral bioavailability or absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are frequently responsible for clinically significant drug interactions[5,6]:

- The CYP enzyme system is responsible for the metabolism of many ARV medications, including several INSTIs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, maraviroc, fostemsavir, and lenacapavir (LEN). CYP3A4 is the most common enzyme responsible for drug metabolism, although 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 responsible for the metabolism of INSTIs, particularly cabotegravir (CAB) and raltegravir. Drugs that induce or inhibit the UGT enzyme can affect the PK of these INSTIs.

Some ARVs have mixed metabolic pathways involving both CYP3A4 and UGT1A1. Notably, the INSTIs bictegravir and dolutegravir (DTG), as well as the capsid inhibitor LEN, are metabolized through both enzyme systems. 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 (i.e., concentrations) 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. When coadministered with ARVs metabolized by the CYP3A4 pathway, the resultant systemic exposure of the ARVs is higher. Importantly, apart from CYP3A4, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. These 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 (statins).

Transporter-Mediated Pharmacokinetic Interactions

Drug transporters are expressed in various tissues, and they play an important role in drug disposition.[7] 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 DDIs is complex, and the clinical significance of some interactions is unclear but is under investigation.

Other Mechanisms of Pharmacokinetic Interactions

Enzymes Involved in Nucleoside Metabolism

Islatravir (ISL) requires intracellular phosphorylation to its active triphosphate form (ISL-TP) to exert its antiviral effect.[8] This activation step and its metabolic pathway create two key interaction considerations:

- **Deoxycytidine kinase (dCK) substrate competition:** Coadministration with other dCK substrates, such as certain nucleoside ARVs (e.g., lamivudine, emtricitabine), **is contraindicated.** Coadministration with nucleoside antimetabolites (e.g., cytarabine) **is not recommended,** as it may reduce ISL-TP formation, potentially compromising therapeutic efficacy.
- **Adenosine deaminase (ADA) inhibition:** Concurrent use of ADA inhibitors (e.g., pentostatin) **is not recommended,** because it may significantly increase ISL plasma concentrations and increase the risk of adverse reactions.

Drug–Drug Interactions With Long-Acting Antiretroviral Medications

As with all antiretroviral therapy, individuals receiving long-acting (LA) ARVs should be regularly monitored for DDIs, including those that may alter the concentrations of the ARVs or the concomitant medications. The extended half-lives of LA ARVs, such as injectable LEN and LA CAB/RPV, introduce unique DDI management challenges not encountered with daily oral regimens, which may complicate both the detection and resolution of DDIs. Electronic medical records may not detect or alert clinicians regarding these interactions because LA ARV medications can be listed outside of current medication lists or may be ordered as one-time injections as opposed to continuous therapy. Patients should be counseled to promptly report any new medication changes so that interactions can be identified and addressed in a timely manner.

The approach for managing a particular DDI may differ depending on the scenario: whether the LA ARV medication is being initiated in a person already receiving stable concomitant medications, whether new medications are being introduced to a person already on LA ARV medications, or if the LA ARV medication is discontinued. Each scenario requires a tailored approach, including potential dose adjustment, alternative drug selection, and development of a monitoring strategy.

For example, LEN can increase concentrations of certain concomitant medications initiated within 9 months of the last LEN dose.[9] Thus, the DDI risk of LA ARVs may persist well into the post-discontinuation period and may not be immediately apparent to clinicians. Clinicians should screen for potential DDIs throughout the period of residual drug exposure as described in the relevant prescribing information for LA ARV medications.

Finally, if oral ARV bridging is required due to a missed LA ARV injection, the DDI profile of the bridging regimen should be reviewed and managed accordingly.

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 medication and another medication is likely to result in a clinically important DDI, 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 medications are commercially available; however, results may take 1 week or longer to be reported. When interpreting assay results, clinicians should consider the person's medication adherence, the timing of the person's last ARV dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If available, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take, which may include further monitoring and/or dosage adjustments.

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) medication and/or the interacting drug. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs; 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: Information regarding P-glycoprotein, CYP substrate, inhibitor, and inducer status and UGT1A1 is referenced from product labels. N/A indicates that there are no clinically relevant interactions by the mechanism. Identified mechanisms are specific to the ARV medications described in the row and may not be reflective of complete ARV regimens. Some older ARVs—unboosted atazanavir, fosamprenavir, nelfinavir, nevirapine, tipranavir, and oral zidovudine—are not commonly used in clinical practice and/or are no longer recommended by the Panel for the Use of Antiretroviral Agents in Adults and Adolescents With HIV for use in adults and adolescents; therefore, they are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels or the Liverpool HIV Drug Interaction Checker 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 (IM and PO)	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

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
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
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 (IM and PO)	**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
ISL[a]	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
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 (PO and SQ)	N/A	N/A	Substrate, inhibitor	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
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a] See subsection regarding ISL interactions.

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 P450; 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; IM = intramuscular; INSTI = integrase strand transfer inhibitor; ISL = islatravir; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; Mg = magnesium; MVC = maraviroc; N/A = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; P-gp = P-glycoprotein; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase; Zn = zinc

Knowledge Gaps

- Research is needed to understand optimal clinical management strategies for DDIs between LA injectable ARV medications and key medication categories (e.g., commonly prescribed medications, CYP3A4 inducers).
- More research is needed to evaluate DDIs between ARV medications and newer anti-tuberculosis medications.
- Research is needed to determine the clinical utility of TDM for management of ARV drug interactions (including LA ARV medications) in specific clinical scenarios, such as renal or hepatic impairment, obesity, and pregnancy.
- Research is needed to develop, test, and implement novel modalities for TDM of ARVs (e.g., alternate biological matrices, including dried blood spot and urine) that can inform DDI management.
- Research is needed to characterize the PK and clinical impact of multidrug interactions occurring when more than two medications are used concomitantly with ART.
- More research is needed to understand transporter-mediated ARV DDIs and their clinical significance.
- More research is needed to understand real-world prescribing practices (e.g., via observational studies), whether they follow established dosing and monitoring recommendations for ARV DDIs with high-risk medications (e.g., narrow therapeutic index drugs or high potential for adverse events), and the outcomes of those practices in order to implement strategies for safely prescribing ARV medications.
- More research is needed to understand if sex may influence the adverse clinical outcomes of ARV DDIs and to inform any dosing strategies that can minimize these effects.
- Research is needed to facilitate the translation and application of DDI study findings (particularly PK modeling studies) to clinical practice for optimal interaction management.

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APPENDIX A. DRUG CHARACTERISTICS TABLES

Appendix A, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Updated: September 24, 2026
Reviewed: September 24, 2026

This 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 A, 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 generic name within each class.

Generic Name (Abbreviation) *Trade Name*	**ARV Drugs Included in the Regimen**	**Dosing Recommendation[a]**
INSTI Plus Two NRTIs		
Bictegravir/Tenofovir Alafenamide/Emtricitabine (BIC/TAF/FTC) *Biktarvy*	BIC 50 mg/TAF 25 mg/FTC 200 mg	One tablet PO once daily
Dolutegravir/Abacavir/Lamivudine (DTG/ABC/3TC) *Triumeq*	DTG 50 mg/ABC 600 mg/3TC 300 mg	One tablet PO once daily
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	EVG 150 mg/COBI 150 mg/TAF 10 mg/FTC 200 mg	One tablet PO once daily with food
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/c/TDF/FTC) *Stribild*	EVG 150 mg/COBI 150 mg/TDF 300 mg/ FTC 200 mg	One tablet PO once daily with food

Appendix A, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Generic Name (Abbreviation) *Trade Name*	**ARV Drugs Included in the Regimen**	**Dosing Recommendation**[a]
INSTI Plus One NRTI		
Dolutegravir/Lamivudine (DTG/3TC) *Dovato*	DTG 50 mg/3TC 300 mg	One tablet PO once daily
INSTI Plus One NNRTI		
Cabotegravir/Rilpivirine (CAB/RPV) *Cabenuva*	**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 monthly and RPV 600 mg/2 mL IM monthly **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
Dolutegravir/Rilpivirine (DTG/RPV) *Juluca*	DTG 50 mg/RPV 25 mg	One tablet PO once daily with food
NNRTI Plus Two NRTIs		
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine (DOR/TDF/3TC) *Delstrigo*	DOR 100 mg/TDF 300 mg/3TC 300 mg	One tablet PO once daily

Appendix A, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Generic Name (Abbreviation) *Trade Name*	**ARV Drugs Included in the Regimen**	**Dosing Recommendation**[a]
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine (EFV/TDF/FTC) *Generic Only*	EFV 600 mg/TDF 300 mg/FTC 200 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Generic Only*	EFV 600 mg/TDF 300 mg/3TC 300 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
Rilpivirine/Tenofovir Alafenamide/Emtricitabine (RPV/TAF/FTC) *Odefsey*	RPV 25 mg/TAF 25 mg/FTC 200 mg	One tablet PO once daily with food
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine (RPV/TDF/FTC) *Complera or Generic*	RPV 25 mg/TDF 300 mg/FTC 200 mg	One tablet PO once daily with food
NNRTI Plus One NRTI		
Doravirine/Islatravir (DOR/ISL) *Idvynso*	DOR 100 mg/ISL 0.25 mg	One tablet PO once daily
PI (Boosted) Plus Two NRTIs		
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (DRV/c/TAF/FTC) *Symtuza*	DRV 800 mg/COBI 150 mg/TAF 10 mg/ FTC 200 mg	One tablet PO once daily with food

[a] For dose adjustments in people with renal or hepatic insufficiency, see Appendix B. When no food restriction is listed, the product can be taken with or without food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; c or COBI = cobicistat; 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; ISL = islatravir; 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 A, Table 2. Nucleoside Reverse Transcriptase Inhibitor–Based, Fixed-Dose Combination Tablets for Use as Part of an Antiretroviral Regimen

Updated: September 25, 2025
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This 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; oral ZDV is no longer recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents due to the potential for serious adverse effects. Please see the class-specific drug characteristics tables (Appendix A, 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 generic name.

Generic Name (Abbreviation) *Trade Name*	**ARV Drugs Included in the FDC Tablet**	**Dosing Recommendation**[a]
Abacavir/Lamivudine (ABC/3TC) *Generic Only*	ABC 600 mg/3TC 300 mg	One tablet PO once daily
Tenofovir Alafenamide/Emtricitabine (TAF/FTC) *Descovy*	TAF 25 mg/FTC 200 mg	One tablet PO once daily
Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) *Truvada* **Note:** Generic product available.	TDF 300 mg/FTC 200 mg	One tablet PO once daily
Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) *Cimduo*	TDF 300 mg/3TC 300 mg	One tablet PO once daily

[a] For dose adjustments in people with renal or hepatic insufficiency, see Appendix B. 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; PO = orally; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix A, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

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This 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. Oral zidovudine (ZDV) is no longer recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents due to the potential for serious adverse effects. 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 products are available.	**Ziagen** • 20-mg/mL oral solution **Generic** • 300-mg tablet • Also available as FDC with 3TC **FDC Tablets That Contain ABC**[c] • ABC/3TC **STRs That Contain ABC**[d] • Triumeq (DTG/ABC/3TC)	*Tablet* • ABC 600 mg PO once daily, *or* • ABC 300 mg PO twice daily See Appendix A, 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).	1.5 hours/ 12–26 hours	ABC is **contraindicated** in people who test positive for HLA-B*5701 due to an increased risk of HSRs. HLA screening should be done before initiating ABC. For people with a history of HSRs, rechallenge is **contraindicated.** 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). Evidence increasingly supports a relationship between ABC and major CV events.

Appendix A, 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* **Note:** Generic products are available.	**Emtriva** • 200-mg hard gelatin capsule • 10-mg/mL oral solution **Generic** • 200-mg capsule • Also available as FDC with TDF **FDC Tablets That Contain FTC**[c] • Descovy (TAF/FTC) • Truvada (TDF/FTC) **STRs That Contain FTC**[d] • Biktarvy (BIC/TAF/FTC) • Complera (or generic) (RPV/TDF/FTC) • EFV/TDF/FTC (generic) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Stribild (EVG/c/TDF/FTC) • Symtuza (DRV/c/TAF/FTC)	*Capsule* • FTC 200 mg PO once daily *Oral Solution* • FTC 240 mg (24 mL) PO once daily See Appendix A, Tables 1 and 2 for dosing information for FDC tablets that contain FTC.	86% of FTC dose is excreted renally. See Appendix B 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.
Islatravir (ISL)	ISL is available only as a component of the STR Idvynso (DOR/ISL).[d]	• One tablet PO once daily See Appendix A, Table 1 for dosing information.	ADA-mediated metabolism (approximately 53%)	21 hours/ 186 hours	Diarrhea
Lamivudine (3TC) *Epivir* **Note:** Generic products are available.	**Epivir** • 150-mg and 300-mg tablets • 10-mg/mL oral solution	*Tablet* • 3TC 300 mg PO once daily, *or* • 3TC 150 mg PO twice daily See Appendix A, Tables 1 and 2 for dosing information	70% of 3TC dose is excreted renally. See Appendix B 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 A, 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]
	Generic • 100-mg, 150-mg, and 300-mg tablets • 10-mg/mL oral solution • Also available as FDC with ABC **FDC Tablets That Contain 3TC[c]** • ABC/3TC (generic) • Cimduo (TDF/3TC) **STRs That Contain 3TC[d]** • Delstrigo (DOR/TDF/3TC) • Dovato (DTG/3TC) • EFV/TDF/3TC (generic) • Triumeq (DTG/ABC/3TC)	for FDC tablets that contain 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 A, Tables 1 and 2 for dosing information for FDC tablets that contain TAF.	Metabolized by cathepsin A. See Appendix B 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 A, 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 products are available.	**Viread** • 150-mg, 200-mg, 250-mg, and 300-mg tablets • 40-mg/g oral powder **Generic** • 300-mg tablet • Also available as FDC with FTC **FDC Tablets That Contain TDF**[c] • Cimduo (TDF/3TC) • Truvada (TDF/FTC) **STRs That Contain TDF**[d] • Complera (or generic) (RPV/TDF/FTC) • Delstrigo (DOR/TDF/3TC) • EFV/TDF/FTC (generic) • EFV/TDF/3TC (generic) • Stribild (EVG/c/TDF/FTC)	*Tablet* • TDF 300 mg PO once daily *Oral Powder* • 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 A, Tables 1 and 2 for dosing information for FDC tablets that contain TDF.	Renal excretion is the primary route of elimination. See Appendix B 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] When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix A, Table 2 for information about these formulations.

[d] See Appendix A, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; ADA = adenosine deaminase; BIC = bictegravir; BMD = bone mineral density; CV = cardiovascular; DOR = doravirine; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HB = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; ISL = islatravir; PO = orally; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix A, Table 4. Characteristics of Integrase Strand Transfer Inhibitors

Updated: September 12, 2024
Reviewed: September 24, 2026

This table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved integrase strand transfer inhibitor products for adults with HIV. Not all formulations 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]	• One tablet PO once daily See Appendix A, Table 1 for dosing information.	CYP3A4 substrate UGT1A1-mediated glucuronidation	~17 hours	Diarrhea Nausea Headache Weight gain Depression
Cabotegravir (CAB)	**Copackaged IM Regimen** • Cabenuva (CAB plus RPV) **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 A, Table 1 for dosing information for coformulated and copackaged regimens that contain CAB.	UGT1A1 and UGT1A9-mediated glucuronidation	PO: 41 hours IM: 6–12 weeks	**CAB Plus RPV** • Headache • Nausea • Abnormal dreams • Anxiety • Insomnia • Depressive disorders • Hepatotoxicity **IM Formulation Only** • Injection site reactions (e.g., pain, induration, swelling, nodules)

Appendix A, Table 4. 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 mg PO 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 A, 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.
Elvitegravir (EVG)	EVG is only available as a component of STR tablets that also contain COBI, FTC, and either TDF or TAF. **STRs That Contain EVG**[c] • Genvoya (EVG/c/TAF/FTC) • Stribild (EVG/c/TDF/FTC)	**Genvoya and Stribild** • One tablet PO once daily with food. • See Appendix A, Table 1 for dosing information **Genvoya** • See Appendix B for recommendations on dosing in persons with renal insufficiency. **Stribild** • **Not recommended** for people with baseline CrCl <70 mL/min (see Appendix B).	**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)

Appendix A, Table 4. Characteristics of Integrase Strand Transfer Inhibitors

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathways**	**Serum Half-Life**	**Adverse Events**[b]
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 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. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix A, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P450; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HD = high dose; HSR = hypersensitivity reaction; IM = intramuscular; INSTI = integrase strand transfer inhibitor; 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 A, Table 5. Characteristics of Protease Inhibitors

Updated: September 25, 2025
Reviewed: September 24, 2026

This 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* **Note:** Generic products are available.	**Reyataz** • 200-mg and 300-mg capsules • 50-mg oral powder/packet **Generic** • 200-mg and 300-mg capsules **FDCs That Contain ATV** • Evotaz (ATV 300 mg/COBI 150 mg)	**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).	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. 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.

Appendix A, 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 or if taking a nephrotoxic agent (see Appendix B). For dosing recommendations for people who also are receiving H2 antagonists and PPIs, see the Liverpool HIV Drug Interaction Checker.			
Darunavir (DRV) *Prezista* **Note:** Generic products are available.	**Prezista** • 600-mg and 800-mg tablets • 100-mg/mL oral suspension **Generic** • 600-mg and 800-mg tablets **FDCs That Contain DRV** • Prezcobix (DRV 800 mg/COBI 150 mg) **STRs That Contain DRV** • Symtuza (DRV/c/TAF/FTC)	**Prezista** *In People Without Prior ARV Treatment or ARV-Experienced Treatment With No DRV Resistance 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 DRV is not available as an FDC tablet with RTV. 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). See Appendix A, 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 A, 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 products are available. RTV is used at 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 **Generic** • 100-mg tablet Also available as an FDC tablet of LPV/r in both brand (Kaletra) and generic versions	**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.

[b] Also see Table 20.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P450; DRV = darunavir; DRV/c = darunavir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; GI = gastrointestinal; H2 = histamine H2 receptor; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; PK = pharmacokinetic; PO = orally; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT1 = uridine diphosphate glucuronyl transferase 1 family

Appendix A, Table 6. Characteristics of Non-nucleoside Reverse Transcriptase Inhibitors

Updated: September 24, 2026
Reviewed: September 24, 2026

This 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 not recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents due to the potential for serious adverse effects.

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) • Idvynso (DOR/ISL)	• DOR 100 mg PO once daily See Appendix A, Table 1 for dosing information for STRs that contain DOR.	CYP3A4/5 substrate	15 hours	Rash, including Stevens-Johnson syndrome Nausea Dizziness Abnormal dreams
Efavirenz (EFV) **Note:** Generic only	**Efavirenz** (generic) • 600-mg tablet **STRs That Contain EFV**[c] • EFV/TDF/FTC (generic) • EFV/TDF/3TC (generic)	• EFV 600 mg PO once daily on an empty stomach, preferably at or before bedtime See Appendix A, 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, including Stevens-Johnson syndrome Neuropsychiatric symptoms[d] 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* **Note:** Generic products are available.	**Intelence** • 100-mg and 200-mg tablets **Generic** • 100-mg and 200-mg tablets	• 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 HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure), have been reported. Nausea

Appendix A, Table 6. 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* **Note:** Generic product available.	**Edurant** • 25-mg tablet **Generic** • 25-mg tablet **STRs That Contain RPV[c]** • Complera (or generic) RPV/TDF/FTC • Juluca (DTG/RPV) • Odefsey (RPV/TAF/FTC) **Copackaged IM Regimen** • Cabenuva (CAB plus RPV)	• RPV 25 mg PO once daily with food See Appendix A, Table 1 for dosing information for coformulated and copackaged regimens that contain RPV.	CYP3A4 substrate	PO: 50 hours IM: 13–28 weeks	Rash, including Stevens-Johnson syndrome 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. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix A, Table 1 for information about these formulations.

[d] 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; CAB = cabotegravir; CYP = cytochrome P450; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; FTC = emtricitabine; HSR = hypersensitivity reaction; ISL = islatravir; IM = intramuscular; IV = intravenous; PO = orally; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix A, Table 7. Characteristics of the Capsid Inhibitor

Updated: September 24, 2026
Reviewed: September 24, 2026

This 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-gp, CYP3A (minor), UGT1A1 (minor) CYP3A4 inhibitor (moderate) and P-gp inhibitor	Injection site reactions, including nodules, induration, and necrosis Serious injection site reactions (e.g., necrosis and ulcer) may occur when LEN is improperly administered intradermally instead of subcutaneously. Nausea, diarrhea, headache

[a] Also see Table 20.

Key: CYP = cytochrome P450; LEN = lenacapavir; P-gp = P-glycoprotein; PO = orally; SQ = subcutaneous

Appendix A, Table 8. Characteristics of the gp120 Attachment Inhibitor

Updated: May 26, 2023
Reviewed: September 24, 2026

This 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 P450; FTR = fostemsavir; PO = orally; QTc = QT corrected for heart rate

Appendix A, Table 9. Characteristics of the CD4 Post-Attachment Inhibitor

Updated: May 26, 2023
Reviewed: September 24, 2026

This table includes dose recommendations for the U.S. Food and Drug Administration (FDA)–approved CD4 T lymphocyte 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*	• Single-dose 2-mL vial containing IBA 200 mg/1.33 mL (150 mg/mL)	• 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 • Undiluted IBA solution can be given as IV push: over 90 seconds for loading dose and over 30 seconds every 2 weeks for maintenance dose. • 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 A, Table 10. Characteristics of the CCR5 Antagonist

Updated: September 25, 2025
Reviewed: September 24, 2026

This 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* **Note:** Generic products are available.	**Selzentry** • 150-mg and 300-mg tablets • 20-mg/1-mL oral solution **Generic** • 150-mg and 300-mg tablets	• 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, 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.

[b] Also see Table 20.

Key: CYP = cytochrome P450; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = orally; RAL = raltegravir; TPV/r = tipranavir/ritonavir

APPENDIX B. ANTIRETROVIRAL DOSING RECOMMENDATIONS IN ADULTS WITH RENAL OR HEPATIC INSUFFICIENCY

Updated: September 24, 2026
Reviewed: September 24, 2026

These tables include antiretroviral (ARV) products that are not approved by the U.S. Food and Drug Administration (FDA) for use in adolescents with HIV. For information regarding the use of ARV 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.

Renal dosing information for fixed-dose combination products, as well as coformulated and copackaged antiretroviral regimens, is included in the tables below. The older antiretroviral drugs fosamprenavir (FPV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), nevirapine (NVP), tipranavir (TPV), and oral zidovudine (ZDV) have been removed from this table because they are no longer commonly used and/or not recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Please refer to the FDA product labels for these drugs for recommendations on dosing in adults and adolescents with renal or hepatic insufficiency.

Please refer to the National Institute of Diabetes and Digestive and Kidney Diseases Determining Drug Dosing in Adults With Chronic Kidney Disease webpage for a discussion on using estimated creatinine clearance (CrCl) versus estimated glomerular filtration rate (eGFR) in determining renal function. eGFR based on the 2021 Chronic Kidney Disease Epidemiology Collaboration (or CKD-EPI) equation can be determined using this eGFR calculator. In FDA prescribing information, renal dosing recommendations for most ARVs are based on CrCl using the Cockroft-Gault formula.

See the section at the end of this table for criteria for Child-Pugh Classifications.

Generic Name (Abbreviation) *Trade Name*	**Usual Dose**[a]	**Dosing in Adults With Renal Insufficiency**	**Dosing in Adults With Hepatic Impairment**
Nucleoside Reverse Transcriptase Inhibitors			
Abacavir (ABC) *Ziagen*	ABC 300 mg PO twice daily *or* ABC 600 mg PO once daily	No dose adjustment	*Child-Pugh Class A:* ABC 200 mg PO twice daily (use oral solution) *Child-Pugh Class B or C:* **Contraindicated**

Appendix B. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

<table>
<tr><th>Generic Name
(Abbreviation)
Trade Name</th><th>Usual Dose[a]</th><th colspan="3">Dosing in Adults With Renal Insufficiency</th><th>Dosing in Adults With Hepatic Impairment</th></tr>
<tr><td>Abacavir/Lamivudine
(ABC/3TC)</td><td>One tablet PO once daily</td><td colspan="3">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. To allow people to remain on the FDC product, some Panel members use full-dose 3TC. See the 3TC entry for more information.</td><td>Child-Pugh Class A: People with mild hepatic impairment require a dose reduction of ABC (as noted above). Use the individual drugs instead of the FDC tablet in these people.
Child-Pugh Class B or C: Contraindicated due to the ABC component</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>FTC 200-mg capsule PO once daily
or
FTC 240-mg (24-mL) solution PO 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 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.</td><td colspan="3">Dose by Formulation
<table><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49[b]</td><td colspan="2">No dose adjustment.</td></tr><tr><td>15–29
(see Note)</td><td>200 mg every 72 hours</td><td>80 mg every 24 hours</td></tr><tr><td><15 (not on HD)
(see Note)</td><td>200 mg every 96 hours</td><td>60 mg every 24 hours</td></tr><tr><td>On HD[b]</td><td colspan="2">No dose adjustment. On HD days, administer after dialysis.</td></tr></table></td><td>No dose recommendation</td></tr>
</table>

Appendix B. 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**
Lamivudine (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. To allow people to remain on certain ABC and/or DTG-containing FDC products, some Panel members use full-dose 3TC.	**CrCl (mL/min)**	**Epivir Label Dose**	**Alternative Dosed**	No dose adjustment
		30–49[c]	No dose adjustment		
		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	
Tenofovir Alafenamide (TAF) *Vemlidy*	Vemlidy is available as a 25-mg tablet given PO once daily for the treatment of HBV. **Note:** For people with progressively declining renal function, consider avoiding TAF.	**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. On HD days, administer after dialysis.		

Appendix B. 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 /Emtricitabine (TAF/FTC) *Descovy*	TAF for HIV treatment is only available as a component of FDC tablets (i.e., in Biktarvy, Descovy, Genvoya, Odefsey, and Symtuza). • TAF 10 mg PO once daily with EVG/c (Genvoya) or DRV/c (Symtuza) • TAF 25 mg PO once daily in other FDC tablets **Note:** For people with progressively declining renal function, consider avoiding TAF.	**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. On HD days, administer after dialysis.	
Tenofovir Disoproxil Fumarate (TDF) *Viread*	TDF 300 mg PO once daily **Note:** Avoid TDF, if possible, for CrCl <60 mL/min or for people with progressively declining renal function.	**CrCl (mL/min)**	**Dose**	No dose adjustment
		30–49	300 mg every 48 hours	
		10–29	300 mg twice weekly (every 72–96 hours)	
		<10 (not on HD)	No dose 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 **Note:** Avoid TDF, if possible, for CrCl <60 mL/min or for people with progressively declining renal function.	**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. 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 **Note:** Avoid TDF, if possible, for CrCl <60 mL/min.	FDC of TDF/3TC **not recommended** for CrCl <50 or on HD		No dose recommendation
Non-Nucleoside Reverse Transcriptase Inhibitors				
Doravirine (DOR) *Pifeltro*	DOR 100 mg PO once daily	No dose adjustment		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Doravirine/Islatravir (DOR/ISL) *Idvynso*	One tablet PO once daily Dosing in the FDA Prescribing Information utilizes eGFR instead of CrCl based on a study in participants with severe renal impairment, defined as eGFR <30 mL/min/1.73 m^2.	**eGFR (mL/min/ 1.73 m^2)**	**Dose**	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
		≥30	No dose adjustment	
		<30	**Not recommended**	
		HD	No dose recommendation	
Doravirine/Tenofovir Disoproxil Fumarate/ Lamivudine (DOR/TDF/3TC) *Delstrigo*	One tablet PO once daily **Note:** Avoid TDF, if possible, for CrCl <60 mL/min.	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:* No dose recommendation
Efavirenz (EFV)	EFV 600 mg PO once daily on an empty stomach, preferably at bedtime	No dose adjustment		*Child Pugh A:* No dose adjustment; use with caution *Child Pugh B or C:* **Not recommended**
Efavirenz/Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC)	One tablet PO once daily on an empty stomach, preferably at bedtime **Note:** Avoid TDF, if possible, for CrCl <60 mL/min.	FDC of EFV/TDF/FTC **not recommended** if CrCl <50 mL/min or on HD		*Child Pugh A:* No dose adjustment; use with caution *Child Pugh B or C:* **Not recommended**

Appendix B. 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**
Efavirenz/ Tenofovir Disoproxil Fumarate/ Lamivudine (EFV/TDF/3TC)	One tablet PO once daily on an empty stomach, preferably at bedtime **Note:** Avoid TDF, if possible, for CrCl <60 mL/min.	FDC of EFV/TDF/3TC **not recommended** if CrCl <50 mL/min or on HD	*Child-Pugh Class A:* No dose adjustment; use with caution *Child-Pugh Class B or C:* **Not recommended**
Etravirine (ETR) *Intelence*	ETR 200 mg PO twice daily following a meal	No dose adjustment	*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	*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 for one 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 two doses • Continuation phase: RPV 900 mg/ 3 mL IM and CAB 600 mg/3 mL IM every 2 months	CrCl <30 or on HD: No dose adjustment; increase monitoring for adverse events.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

Appendix B. 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 **Note:** For people with progressively declining renal function, consider avoiding TAF.	**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. On HD days, administer after dialysis.	
Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) *Complera*	One tablet PO once daily with food **Note:** Avoid TDF, if possible, for CrCl <60 mL/min.	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	In people with CrCl <30 mL/min: No dose adjustment, monitor closely for adverse effects.		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

Appendix B. 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**
Protease Inhibitors			
Atazanavir (ATV) *Reyataz*	ATV 400 mg PO once daily with food *or* (ATV 300 mg plus RTV 100 mg) PO once daily with food *or* (ARV 400 mg plus RTV 100 mg) PO once daily with food See Appendix A, Table 5 for more detailed dosing information.	**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.**	**For Boosted ATV** • RTV boosting **is not recommended** in people with any degree of hepatic impairment. **For Unboosted ATV** • *Child-Pugh Class A:* No dose adjustment • *Child-Pugh Class B:* ATV 300 mg once daily (unboosted) for people without prior ARV treatment • *Child-Pugh Class C:* **Not recommended**
Atazanavir/Cobicistat (ATV/c) *Evotaz*	One tablet PO once daily with food	**If Used With TDF** • **Not recommended** if CrCl <70 mL/min or if also receiving a nephrotoxic agent **In People on Chronic HD** • **Not recommended** for ARV-experienced people on HD	**Not recommended** in people with any degree of hepatic impairment.
Darunavir (DRV) *Prezista*	**In People Without Prior ARV Treatment or ARV-Experienced Treatment With No DRV Resistance 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	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**

Appendix B. 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**
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 **Note:** For people with progressively declining renal function, consider avoiding TAF.	**CrCl (mL/min)**	**Dose**	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
		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 chronic HD	No dose adjustment. On HD days, administer after dialysis.	
Ritonavir (RTV) *Norvir*	**As a PI-Boosting Agent** • RTV 100–200 mg PO per day with food.	No dose adjustment		Refer to recommendations for the primary (i.e., boosted) PI.

Appendix B. 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**
Integrase Strand Transfer Inhibitors				
Bictegravir/Tenofovir Alafenamide/ Emtricitabine (BIC/TAF/FTC) *Biktarvy*	One tablet PO once daily **Note:** For people with progressively declining renal function, consider avoiding TAF.	**CrCl (mL/min)**	**Dose**	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
		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 chronic HD	No dose adjustment. On HD days, administer after dialysis.	
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	**CrCl (mL/min)**	**Dose**	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
		≥15 mL/min	No dose adjustment	
		<15 mL/min or on HD	No dose recommendation	

Appendix B. 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 IM Plus Rilpivirine IM (CAB IM plus RPV IM) *Cabenuva*	**Monthly Dosing** • Loading dose: CAB 600 mg/3 mL IM for one dose and RPV 900 mg/3 mL IM for one dose • Continuation phase: CAB 400 mg/2 mL IM every 4 weeks and RPV 600 mg/2 mL IM every 4 weeks **Every-2-Months Dosing** • Loading dose: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM monthly for two doses • Continuation phase: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM every 2 months	CrCl <30 or on HD: No dose adjustment; increase monitoring for adverse events.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Dolutegravir (DTG) *Tivicay*	DTG 50 mg PO once daily *or* DTG 50 mg PO twice daily	No dose adjustment	*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. To allow people to remain on the FDC product, some Panel members use full-dose 3TC.[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. 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. To allow people to remain on the FDC product, some Panel members use full-dose 3TC.[d]		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Dolutegravir/ Rilpivirine (DTG/RPV) *Juluca*	One tablet PO once daily with food	CrCl <30 or on HD: No dose adjustment; increase monitoring for adverse events.		*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 **Note:** For people with progressively declining renal function, consider avoiding TAF.	**CrCl (mL/min)**	**Dose**	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
		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 chronic HD	No dose adjustment. On HD days, administer after dialysis.	
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.		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**

Appendix B. 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	**For Isentress** • *Child-Pugh Class A or B:* No dose adjustment • *Child-Pugh Class C:* No dose recommendation **For Isentress HD** • **Not recommended** for people with hepatic impairment.
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	The recommended dose differs based on concomitant medications and potential for drug–drug interactions. See Appendix A, Table 10 for detailed dosing information.	**In People With CrCl <30 mL/min or 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 and Moderate CYP3A Inducers or Potent CYP3A Inhibitors* • **Contraindicated**	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	No dose recommendation
gp-120 Attachment Inhibitor			
Fostemsavir (FTR) *Rukobia*	FTR 600 mg PO twice daily	No dose adjustment	No dose adjustment

Appendix B. 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	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

[a] Refer to Appendix A, 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 incorporate 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 ABC/3TC, 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 adverse events. Serious adverse events, 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 nucleoside reverse transcriptase inhibitors (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. To allow people to remain on certain FDC products, some Panel members use full-dose 3TC.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse effect; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; CrCl = creatinine clearance; CYP = cytochrome P450; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; eGFR = estimated glomerular filtration rate; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug

Appendix B. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency

Administration; FDC = fixed-dose combination; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; HD = hemodialysis; IBA = ibalizumab; IM = intramuscular; ISL = islatravir; IV = intravenous; LEN = lenacapavir; MVC = maraviroc; the Panel = Panel on Antiretroviral Guidelines for Adults and Adolescents; PK = pharmacokinetic; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Child-Pugh Classifications

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 (Mild)	5–6 points
Class B (Moderate)	7–9 points
Class C (Severe)	>9 points

[a] Sum of points for each component of the Child-Pugh Score.

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APPENDIX C. KEY TO ACRONYMS

Updated: September 24, 2026
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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
ddC	zalcitabine
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 or ibalizumab-uiyk

Abbreviation	Definition
IDV	indinavir
ISL	islatravir
ISL-TP	islatravir-triphosphate
LA CAB/RPV	long-acting cabotegravir plus rilpivirine
LEN	lenacapavir
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MASLD	metabolic dysfunction–associated steatotic liver disease
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
TPV	tipranavir
TPV/r	tipranavir/ritonavir
ZDV	zidovudine

General Terms

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
ACA	Affordable Care Act
ACC	American College of Cardiology
ACE	adverse childhood experience
ACTG	AIDS Clinical Trials Group
ADA	adenosine deaminase
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
aHR	adjusted hazard ratio
Al	aluminum
ALT	alanine aminotransferase
AMP	average manufacturer price
anti-HBc	hepatitis B core antibody
anti-HBe	hepatitis B e antibody
anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
ARTAS	Anti-Retroviral Treatment and Access to Services
ARV	antiretroviral
ASAM	American Society of Addiction Medicine
ASP	average sales price
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
ATI	analytical treatment interruption
AUD	alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
AV	atrioventricular
AWP	average wholesale price
AYA	adolescents and young adults

Abbreviation	Definition
BMD	bone mineral density
BMI	body mass index
BMT	bone marrow transplant
BUN	blood urea nitrogen
Ca	calcium
CAP	cost-sharing assistance program
CBC	complete blood count
CCR5	C-C chemokine receptor type 5
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval capsid inhibitor
CKD	chronic kidney disease
Cl	chloride
CMS	Centers for Medicare & Medicaid Services
CMV	cytomegalovirus
CNICS	Center for AIDS Research Network of Integrated Clinical Systems
CNS	central nervous system
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
dCK	deoxycytidine kinase
DDI	drug–drug interaction
DILI	drug-induced liver injury

Abbreviation	Definition
DM	diabetes mellitus
DMPA	depo-medroxyprogesterone acetate
DRESS	drug reaction with eosinophilia and systemic symptoms
DRM	drug resistance mutation
DOT	directly observed therapy
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
eGFR	estimated glomerular filtration rate
EI	entry inhibitor
ESRD	end-stage renal disease
FCP	federal ceiling price
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
Fe	iron
FPL	federal poverty level
GAD	Generalized Anxiety Disorder [test]
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
gp120	glycoprotein 120
GVHD	graft versus host disease
H2	histamine type 2
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

Abbreviation	Definition
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
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIV RNA	HIV viral load
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
HPTN	HIV Prevention Trials Network
HR	hazard ratio
HRSA	Health Resources and Services Administration
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
HSR	hypersensitivity reaction
IC_{50}	median inhibitory concentration
IDSA	Infectious Diseases Society of America
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-7	Interleukin-7
IM	intramuscular
IN	integrase
INSTI	integrase strand transfer inhibitor
IPT	isoniazid preventive therapy
IRA	Inflation Reduction Act
IRIS	immune reconstitution inflammatory syndrome

Abbreviation	Definition
IUD	intrauterine device
IV	intravenous
K	potassium
LA	long-acting
LDL	low-density lipoprotein
LLOD	lower limits of detection
LTBI	latent tuberculosis infection
MACE	major adverse cardiovascular events
MATE1	multidrug and toxic compound extrusion 1
MDMA	methylenedioxymethamphetamine
MDR	multidrug resistant
MDR-TB	multidrug-resistant tuberculosis
MDRP	Medicaid Drug Rebate Program
Mg	magnesium
MHC	major histocompatibility complex
MI	myocardial infarction
MMP	Medication Monitoring Project
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTR	multi-tablet regimen
N/A	not applicable
Na	sodium
NADAC	National Average Drug Acquisition Cost
NASTAD	National Alliance of State & Territorial AIDS Directors
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRT	nicotine replacement therapy
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NTD	neural tube defect
OARAC	Office of AIDS Research Advisory Council
OBR	optimized background regimen
OCT2	organic cation transporter 2

Abbreviation	Definition
OI	opportunistic infection
OR	odds ratio
OTP	opioid treatment program
OUD	opioid use disorder
P	phosphorus
P-gp	p-glycoprotein
PAP	patient assistance program
PBM	pharmacy benefit manager
PCE	Pooled Cohort Equations
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
PEP	post-exposure prophylaxis
PHQ	Patient Health Questionnaire
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
PREVENT	Predicting Risk of CVD EVENTs
PTH	parathyroid hormone
QTc	QT corrected for heart rate
RA	receptor agonist
RAPID	Rapid ART Program Initiative for HIV Diagnoses
REPC	Retention through Enhanced Personal Contact
RNA	ribonucleic acid
RT	reverse transcriptase
RWHAP	Ryan White HIV/AIDS Program
SAMHSA	Substance Abuse and Mental Health Services Administration

Abbreviation	Definition
SCr	serum creatinine
SDOH	social determinants of health
SJS	Stevens-Johnson syndrome
SMR	sexual maturity rating
SOT	solid organ transplantation
SPT	skin patch test
SQ	subcutaneous
SSP	syringe service program
STI	sexually transmitted infection
STR	single-tablet regimen
SUD	substance use disorder
TasP	treatment as prevention
TB	tuberculosis
TC	total cholesterol
TDM	therapeutic drug monitoring
TDR	transmitted drug resistance
TEN	toxic epidermal necrolysis
TG	triglyceride
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
USPSTF	U.S. Preventive Services Task Force
UW	University of Washington
VAT	visceral adipose tissue
WAC	wholesale acquisition cost
WBC	white blood cell
WHO	World Health Organization
Zn	zinc

Study and Trial Names

Acronym/Abbreviation	Name
ACTG	Advancing Clinical Therapeutics Globally
ADVANCE	Assessing Donor Variability And New Concepts in Eligibility
ANRS	National Agency for AIDS Research (France)
ARDENT	AIDS Clinical Trial Group study A5257
ARTEMIS	Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study
ATHENA	AIDS Therapy Evaluation in the Netherlands
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
BRAAVE	B/F/TAF Regimen for African Americans with HIV and Virologically Suppressed/Treatment Experienced
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
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
FLAIR	First Long-Acting Injectable Regimen
LATITUDE	Long-Acting Therapy to Improve Treatment Success in Daily LifE
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NADIA	Nucleosides And Darunavir/Dolutegravir In Africa
PARTNER	Partners of People on ART: a New Evaluation of the Risks
RESPOND	International Cohort Consortium of Infectious Disease
REPRIEVE	Randomized Trial to Prevent Vascular Events in HIV
SMART	Strategies for Management of Antiretroviral Therapy
SOLAR	Switch Onto Long-Acting Regimen
STaR	Study of Treatment and Reproductive Outcomes
START	Strategic Timing of AntiRetroviral Treatment
TEMPRANO	Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults
THRIVE	Targeting HIV Retention and Improved Viral Load Through Engagement
VACS	Veterans Aging Cohort Study
WIHS	Women's Interagency HIV Study