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 Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

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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 Clinical Info website (https://clinicalinfo.hiv.gov/).

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What's New in the Guidelines

Updated: September 21, 2022
Reviewed: September 21, 2022

Selection of Antiretroviral Therapy for Individuals Who Acquire HIV After Having Received Long-Acting Cabotegravir for Pre-Exposure Prophylaxis

In this update, several sections of the guidelines have been revised with discussions on factors that clinicians should consider when selecting an antiretroviral (ARV) regimen for individuals who acquire HIV after having received long-acting cabotegravir (CAB-LA) for HIV pre-exposure prophylaxis (PrEP). Because of the long half-life of CAB-LA, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends performing genotypic resistance testing, including testing for integrase resistance, before starting antiretroviral therapy (ART). If resistance testing results are not available before ART initiation, the Panel recommends initiating a boosted darunavir regimen while awaiting results confirming no resistance to the integrase strand transfer inhibitor (INSTI) drug class. The sections updated with this new information include the following:

- Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy
- Drug-Resistance Testing
- What to Start
- Early (Acute and Recent) HIV Infection

Dolutegravir and Neural Tube Defects

Previously, the Tsepamo study from Botswana reported a higher prevalence of neural tube defects (NTDs) in women who received dolutegravir (DTG) during conception than with other ARV drugs. An updated report from the same study showed that the prevalence of NTDs is not significantly different from those on non-DTG regimens. For persons of childbearing potential who are trying to conceive, DTG-based regimens are among the recommended options for most individuals initiating ART. The following sections have been updated with this new information:

- What to Start
- Women with HIV
- Transgender People and HIV

Laboratory Testing

The Panel updated the following sections relating to laboratory tests to be done at the time of ART initiation and the frequency of monitoring during follow-up:

- Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy

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

Drug-Resistance Testing

This section has been updated with two key new recommendations:

- The Panel now recommends drug-resistance testing for 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.
- The Panel previously recommended that resistance testing should be done within 4 weeks of discontinuation of an ARV regimen. However, 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 persons who have experienced virologic failure on a regimen of long-acting cabotegravir and rilpivirine (RPV) or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation **(AIII).**

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

This section has been revised with the following key updates:

- The Panel recommends that for regimen optimization in the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, two NRTIs—tenofovir alafenamide or tenofovir disoproxil fumarate plus emtricitabine (FTC) or lamivudine (3TC)—should be included in the regimen with a fully active drug that has a high resistance barrier, such as DTG, boosted darunavir **(BIII),** or bictegravir **(CIII).**
- The Panel recommends that pregnant persons who present to care on CAB-LA and RPV should be switched to a *Preferred* or an *Alternative* three-drug ARV regimen recommended for use in pregnancy per the Perinatal Guidelines **(AIII).**

Virologic Failure

This section has been updated to harmonize with the recommendations in the Drug-Resistance Testing section of the guidelines with regard to drug-resistance testing in patients in a failing long-acting ARV regimen and recommendations for resistance testing in patients with HIV viral load >200 copies/mL. The section also added clinical trial data from the DAWNING and NADIA studies, in assessing the roles of an INSTI or boosted protease inhibitor–based regimen in patients with failure to first-line non-nucleoside reverse transcriptase inhibitor–based regimens.

Adherence to the Continuum of Care

This section continues to stress the importance of assessing adherence and assisting patients to ensure uninterrupted access to treatment and care. The section also noted that the Panel **recommends against** the use of the long-acting ART regimen of intramuscular CAB and RPV in people who have detectable viral load due to suboptimal adherence to ART and who have ongoing challenges with retention in HIV care, except in a clinical trial **(AIII).**

Other Updates

Minor updates have been made to the following sections:

- Baseline Evaluation
- Hepatitis B Virus/HIV Coinfection
- Hepatitis C Virus/HIV Coinfection
- Cost Considerations and Antiretroviral Therapy

September 1, 2022

Drug–Drug Interactions Tables

- The Panel updated the Drug–Drug Interactions tables (Tables 24a–f) with guidance on the interaction potentials between antiretroviral drugs and antiviral drugs (brincidofovir, cidofovir, or tecovirimat) that are currently being used to treat mpox.

January 20, 2022

Early (Acute and Recent) HIV Infection

- In the previous version of the guidelines, the Panel suggested that an HIV RNA level of <10,000 copies/mL in a person suspected to have acute HIV may represent a false-positive test result. The section was updated to revise this threshold. The Panel noted that given the improved sensitivity and specificity of current HIV RNA tests in the presence of compatible symptoms or exposure history, even a low HIV RNA concentration (e.g., <3,000 copies/mL) in the setting of negative or indeterminate HIV antibody test result may represent acute HIV. The Panel noted that, in rare cases, an HIV RNA <3,000 copies/mL may represent a false-positive quantitative test result. In that case, repeat testing should be done to confirm the diagnosis.
- In this revision, the Panel also provided updated information regarding diagnosis of acute HIV in individuals who are receiving PrEP and subsequent initiation of ART.

Discontinuation or Interruption of Antiretroviral Therapy

- This section has been updated to include discussions regarding discontinuation or interruption of long-acting antiretroviral drugs, including ibalizumab and the intramuscular formulations of CAB and RPV. The section also includes discussions regarding steps to take before and during ART interruption for people with HIV who participate in clinical trials that involve analytical treatment interruptions.

Panel Roster

Updated: September 21, 2022
Reviewed: September 21, 2022

Members and Consultants of the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents

These guidelines were developed by the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (a working group of the Office of AIDS Research Advisory Council).

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Updated: May 24, 2022
Reviewed: May 24, 2022

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 March 1, 2021 to February 28, 2022

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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 March 1, 2021 to February 28, 2022 (continued)

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Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents: Financial Disclosure for Companies Related to HIV Treatment or Diagnostics for the Period March 1, 2021 to February 28, 2022 (continued)

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Key: C = Co-Chair; ES = Executive Secretary; M = Member; N/A = not applicable

Introduction

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Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition, with life expectancy approaching that for people without HIV.[1,2] ART is also highly effective at preventing sexual transmission of HIV in patients who have adequately suppressed viral loads.[3-5] Lack of viral load suppression is mostly due to undiagnosed HIV infection and failure to link or retain patients with HIV in care.

The U.S. Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The Panel's primary goal is to provide HIV care practitioners with recommendations that are based on current knowledge of the antiretroviral (ARV) drugs that are used to treat adults and adolescents with HIV in the United States. The Panel reviews new evidence and updates recommendations when needed. These guidelines include recommendations on baseline laboratory evaluations, treatment goals, benefits of ART and considerations when initiating therapy, choice of the initial regimen for ART-naive people with HIV, ARV drugs or combinations to avoid, management of treatment failure, optimizing ARV regimens, management of adverse effects and drug interactions, and special ART-related considerations in specific populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV to provide recommendations for adolescents at different stages of growth and development. Recommendations for ARV regimens in these guidelines are most appropriate for postpubertal adolescents (i.e., those with sexual maturity ratings [SMR] of 4 and 5). Clinicians should follow recommendations in the Pediatric Antiretroviral Guidelines when initiating ART in adolescents with an SMR of 3 or lower. For recommendations related to pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention.[6]

These guidelines represent current knowledge regarding the use of ARV drugs. Because the science of HIV evolves rapidly, the availability of new agents and new clinical data may change therapeutic options and preferences. Information included in these guidelines may not always be consistent with approved labeling for the specific drugs or indications, and the use of the terms "safe" and "effective" may not be synonymous with the U.S. Food and Drug Administration–defined legal standards for drug approval. The Panel frequently updates the guidelines (current and archived versions of the guidelines are available on the Clinical Info website). However, updates to the guidelines may not keep pace with the release of new data, and the guidelines cannot offer guidance on care for all patients. Patient management decisions should be based on clinical judgement and attention to unique patient circumstances.

The Panel recognizes the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of ART and encourages both the development of protocols and patient participation in well-designed Institutional Review Board–approved clinical trials.

HIV Expertise in Clinical Care

Several studies have demonstrated that overall outcomes in patients with HIV are better when care is delivered by clinicians with HIV expertise (e.g., those who have cared for a large group of patients with HIV),[7-11] reflecting the complexity of HIV transmission and its treatment. Appropriate training, continuing education, and clinical experience are all components of optimal care. Providers who do not have this requisite training and experience should consult HIV experts when needed.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents for the treatment of HIV in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 50 voting members who have expertise in HIV care and research and includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Health Resource and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are nongovernmental scientific members. The Panel also includes four to five community members with knowledge of HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open call for nominations. Each member serves on the Panel for a 4-year term, with an option for reappointment for an additional term. See the Panel Roster for a list of current Panel members.
Financial disclosure	All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used to manage HIV infection. The latest version of the Financial Disclosure list is available on the Clinical Info website.
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are based on studies published in peer-reviewed journals or data available in FDA drug labels. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in Table 2 below
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the section's area of interest. The working groups synthesize available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Other guidelines	These guidelines focus on antiretroviral therapy (ART) for adults and adolescents with HIV. For a more detailed discussion on the use of ART in children and prepubertal adolescents (those with sexual maturity ratings of 1 to 3), clinicians should refer to the Pediatric Antiretroviral Guidelines. These guidelines also include a brief discussion on the management of persons of childbearing potential and pregnant persons. For more details on the use of ARV drugs during pregnancy, see the Perinatal Guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety or efficacy data, or other information relating to ARV drugs that may have an impact on the clinical care of people with HIV. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the Clinical Info website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the Clinical Info website.
Public comments	A 2-week public comment period follows the release of the updated guidelines on the Clinical Info website. The Panel reviews comments to determine whether additional revisions to the guidelines are indicated. The public also may submit comments to the Panel at any time at HIVinfo@NIH.gov.

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation statement includes a letter **(A**, **B**, or **C)** that represents the strength of the recommendation and a Roman numeral **(I**, **II**, or **III)** that represents the quality of the evidence that supports the recommendation (see Table 2 below).

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement B: Moderate recommendation for the statement C: Weak recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes III: Expert opinion

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Baseline Evaluation

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Every patient with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of this initial evaluation are to confirm the diagnosis of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and initiate care as recommended in the HIV Medicine Association of the Infectious Diseases Society of America's (HIVMA/IDSA) Primary Care Guidance for Persons with HIV[1] and the Adult and Adolescent Opportunistic Infections Guidelines.[2] The initial evaluation also should include discussion of the benefits of antiretroviral therapy (ART) for the patient's health and to prevent HIV transmission, as well as strategies to optimize care engagement and treatment adherence **(AIII).** Information obtained in this baseline evaluation then can be used to define treatment management goals and plans. The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART at the time of diagnosis (when possible) or as soon as possible afterward to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, improve the rate of virologic suppression, and reduce HIV transmission **(AII).**

The following laboratory tests performed during initial patient visits can be used to stage HIV progression and to assist in the selection of antiretroviral (ARV) drug regimens:

- HIV antigen/antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) **(AI)**
- CD4 T lymphocyte (CD4) cell count **(AI)**
- Plasma HIV RNA (viral load) **(AI)**
- Complete blood count; chemistry profile, including glucose, blood urea nitrogen and creatinine, liver enzymes and bilirubin, urinalysis, and serologies for hepatitis A, B, and C viruses **(AIII)**
  - If random blood glucose level is abnormal, repeat fasting
- Serum lipids (if random levels are abnormal, fasting lipids should be obtained)
- HLA-B*5701 test (if abacavir is being considered) **(AI)**
- Genotypic drug-resistance testing **(AII).** Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive people should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern in people with newly diagnosed HIV or in people who acquired HIV after receipt of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), testing for mutations in the integrase gene also should be performed.
- For patients who have HIV RNA levels <1,000 copies/mL, viral amplification for drug-resistance testing should still be performed; however, it may not always be successful **(BII)** (see Drug-Resistance Testing).

In addition, other tests (including screening tests for sexually transmitted infections, opportunistic infections, and cancer) should be performed as recommended in the HIVMA/IDSA's Primary Care Guidance for Persons with HIV[1] and the Adult and Adolescent Opportunistic Infections Guidelines.[2]

Many clinics have adopted a rapid start policy to initiate ART on the day of HIV diagnosis in order to increase ART uptake and engagement in care and to accelerate the time to viral suppression. Rapid ART initiation also reduces the time during which people with newly diagnosed HIV can transmit HIV. Prior to ART initiation, HIV infection should be confirmed. HIV RNA and CD4 count also should be obtained, but results need not be available before starting ART. CD4 count will determine the need for prophylaxis for certain opportunistic infections.

- If available, results of safety testing—such as complete blood count, renal function tests, and liver enzymes—should be reviewed. If safety test results are not available, ART can still be started, but a clinician should review the results as soon as possible.
- Genotypic resistance testing for RT and PR (and INSTI resistance testing if patient has a history of CAB PrEP use or if INSTI transmission is suspected) should be obtained before ART initiation. It is not necessary to delay ART until results are available, but results should be reviewed as soon as possible in order to make adjustments to the regimen, if needed.
- Screening for viral hepatitis should be done before starting ART, and if ART initiation occurs before results are available, a regimen that has activity against hepatitis B virus should be selected.
- In patients who do not have reliable methods of contact, rapid ART may be initiated, with a plan for a return clinic visit soon after ART initiation to review test results.
- Screening for sexually transmitted infections should, ideally, occur at the initial visit, but results do not need to be available before starting ART.

For previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete ARV history (including drug-resistance testing results, if available), preferably through the review of past medical records. A complete immunization history (including for SARS-CoV-2) also should be obtained. Newly diagnosed patients also should be asked about any prior use of ARV agents for prevention of HIV infection.

People with HIV often must cope with many social, psychiatric, and medical issues that are best addressed through a patient-centered, multidisciplinary approach. The baseline evaluation should include consideration of the patient's readiness for ART, including an assessment of substance use (including tobacco use), social support, mental health, medical comorbidities, economic factors (e.g., unstable housing, food instability), medical insurance status and adequacy of coverage, and other factors that are known to impair adherence to ART and increase the risk of HIV transmission. Once evaluated, these factors should be managed accordingly. The baseline evaluation also should include a discussion of risk reduction and disclosure to sexual and/or needle-sharing partners, especially with untreated patients who are still at high risk of HIV transmission. People with HIV should be informed that maintaining a plasma HIV RNA of <200 copies/mL, including any measurable value below this threshold, with ART prevents sexual transmission of HIV to their partners **(AII).** Patients may recognize this concept as Undetectable = Untransmittable or U=U.

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Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring of People with HIV Receiving Antiretroviral Therapy

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Several laboratory tests are important for initial evaluation of people with HIV upon entry into care. Some tests should be performed before and after initiation or modification of antiretroviral therapy (ART) to assess the virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs. Table 3 below outlines recommendations from the Panel on Antiretroviral Guidelines for Adults and Adolescents on the frequency of testing. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are used to monitor people with HIV: plasma HIV RNA (viral load) to assess level of HIV viremia and CD4+ T lymphocyte cell count (or CD4 count) to assess immune function. Standard (reverse transcriptase and protease) genotypic drug-resistance testing should be used to guide selection of an ARV regimen; if transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern or for people who acquired HIV after taking long-acting cabotegravir as pre-exposure prophylaxis, testing also should include the integrase gene (see Drug-Resistance Testing). For guidance on the choice of ARV regimens before drug-resistance testing results become available, clinicians should consult the What to Start section. A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure that occurs while a patient is receiving a CCR5 antagonist. HLA-B*5701 testing should be performed before initiation of abacavir (ABC) to reduce the risk of hypersensitivity reaction, and HLA-B*5701-positive patients should not be prescribed ABC. Patients should be screened for hepatitis B and hepatitis C virus infections before initiating ART and, if indicated, periodically after ART initiation, because treatment of these coinfections may affect the choice of ART and likelihood of drug-induced hepatotoxicity. The rationale for and utility of some of these laboratory tests are discussed in the corresponding sections of the guidelines.

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
HIV Antigen/ Antibody Test	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√		√[d] If CD4 count is <300 cells/mm^3	√ During the first 2 years of ART, if CD4 count is ≥ 300 cells/mm^3	√ After 2 Years on ART with Consistently Suppressed Viral Load *CD4 Count 300–500 cells/mm^3* • Every 12 months *CD4 Count >500 cells/mm^3* • CD4 count monitoring is optional.	√	√	√ Every 3–6 months

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
HIV Viral Load	√	√	√[e]	√[f]	√[f]		√	√	Repeat testing is optional.
Genotypic Resistance Testing (PR/RT Genes)[g]	√	√					√	√	√
Genotypic Resistance Testing (Integrase Genes)[g]	√ If transmitted INSTI resistance is suspected or if there is a history of CAB-LA use for PrEP	√[f] If transmitted INSTI resistance is suspected or if there is a history of INSTI use					√ If there is a history of INSTI use	√ If there is a history of INSTI use	

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist, or for patients with virologic failure on a CCR5 antagonist	√	
HLA-B*5701 Testing		√ If considering ABC							
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)[h,i,j]	√	In patients not immune to HBV, consider retesting if switching to a regimen that does not contain TDF or TAF.						√ Including before starting HCV DAA	

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Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
Hepatitis C Screening (HCV antibody or, if indicated, HCV RNA)[k]	√					√ Repeat HCV screening for at-risk patients[l]		√	
Basic Metabolic Panel[m,n]	√	√	√		√			√	√ Every 6–12 months
ALT, AST, Total Bilirubin	√	√	√		√			√	√ Every 6–12 months
CBC with Differential[o]	√	√		√ When monitoring CD4 count (if required by lab)	√ When monitoring CD4 count (if required by lab)	√ When no longer monitoring CD4 count		√	
Lipid Profile[p]	√		Consider 1–3 months after ARV initiation or modification			√ If normal at baseline but with CV risk		If normal at baseline, every 5 years or if clinically indicated	

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	4 to 8 Weeks After ART Initiation or Modification	Every 3 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation Is Delayed[c]
Random or Fasting Glucose[q]	√	√					√	√	
Urinalysis[n,r]	√							√ E.g., in patients with CKD or DM	
Pregnancy Test[s]	√	√						√	

[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Medicine Association of the Infectious Diseases Society of America's (HIVMA/IDSA) Primary Care Guidance for Persons with HIV for other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

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

[c] ART is indicated for all people with HIV and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

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

[e] If HIV RNA is detectable at 4–8 weeks, repeat testing every 4–8 weeks until viral load is suppressed to <50 copies/mL. Thereafter, repeat testing every 3–6 months.

[f] For patients on ART, viral load typically is measured every 3–6 months. More frequent monitoring may be considered in individuals having difficulties with ART adherence or at risk for nonadherence. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 1 year, monitoring can be extended to 6-month intervals.

[g] Standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the PR and RT genes. If transmitted INSTI resistance is a concern, or if a person has a history of INSTI use as PrEP or treatment, or a person presents with viremia while on an INSTI, providers also should test for resistance mutations in the IN gene. In ARV-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if drug-resistance testing was performed at entry into care. In

patients with virologic suppression who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; see the Drug-Resistance Testing section for a discussion of the potential limitations and benefits of proviral DNA assays in this situation. Results from prior drug-resistance testing should be considered because they can be helpful in constructing a new regimen.

[h] If a patient has HBV infection (as determined by a positive HBsAg or HBV DNA test result), TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections (see the Hepatitis B Virus/HIV Coinfection section).

[i] If HBsAg, HBsAb, and HBcAb test results are negative, HBV vaccine series should be administered. Refer to the HIVMA/IDSA's Primary Care Guidance for Persons with HIV and the Adult and Adolescent Opportunistic Infection Guidelines for detailed recommendations.[1,2]

[j] Most patients with isolated HBcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load test for confirmation. If the HBV viral load test is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If the test is negative, the patient should be vaccinated. Refer to the HIVMA/IDSA's Primary Care Guidance for Persons with HIV and the Adult and Adolescent Opportunistic Infection Guidelines for more detailed recommendations.[2]

[k] The HCV antibody test may not be adequate for screening in the setting of recent HCV infection (acquisition within the past 6 months) or advanced immunodeficiency (CD4 count <100 cells/mm^3). HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative patients with elevated ALT may need HCV RNA testing.

[l] Injection drug users, people with a history of incarceration, men with HIV who have unprotected sex with men, and people with percutaneous/parenteral exposure to blood in unregulated settings are at risk of HCV infection.

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

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

[o] CBC with differential should be done when a CD4 count is performed. When CD4 count is no longer being monitored, the recommended frequency of CBC with differential is once a year. More frequent monitoring may be indicated for people receiving medications that potentially cause cytopenia (e.g., TMP-SMX).

[p] If random lipids are abnormal, fasting lipids should be obtained. Consult the American College of Cardiology/American Heart Association's 2018 Guideline on the Management of Blood Cholesterol for diagnosis and management of patients with dyslipidemia.[4]

[q] If random glucose is abnormal, fasting glucose should be obtained. HbA1C is no longer recommended for diagnosis of diabetes in people with HIV on ART (see the American Diabetes Association Guidelines).[5]

[r] Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

[s] For persons of childbearing potential.

Key: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CAB-LA = cabotegravir long-acting; CBC = complete blood count; CD4 = CD4 T lymphocyte; CKD = chronic kidney disease; Cl = chloride; Cr = creatinine; CV = cardiovascular; DAA = direct-acting antiviral; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; HbA1C = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO_3 = bicarbonate; HCV = hepatitis C virus; IN = integrase; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; P = phosphorus; PR = protease; PrEP = pre-exposure prophylaxis; RT = reverse transcriptase; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TMP-SMX = trimethoprim-sulfamethoxazole

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

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HIV RNA (viral load) and CD4 T lymphocyte cell (CD4) count are the two surrogate markers of antiretroviral therapy (ART) responses and HIV disease progression that have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.[1] The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART.

CD4 count provides information on the overall immune function of a person with HIV. Measurement of CD4 count is particularly useful **before** initiation of ART to establish the need for the initiation of opportunistic infection (OI) prophylaxis and to assess the urgency to initiate ART; and **after** initiation of ART to assess immunologic response and to establish the need for discontinuation of OI prophylaxis.

The management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. ART is now recommended for all patients with HIV regardless of their viral load or CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). In the past, the clinical practice supported by treatment guidelines was generally to monitor both CD4 count and viral load concurrently. However, because most patients with HIV in care now receive ART, the rationale for frequent CD4 count monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed in the following sections.

Plasma HIV-1 RNA (Viral Load) Monitoring

Viral load is the most important indicator of initial and sustained response to ART and should be measured in all patients with HIV at entry into care **(AI),** at initiation of therapy **(AI),** and on a regular basis thereafter. For those patients who choose to delay therapy or remain untreated for whatever reason, repeat viral load testing while not on ART is optional **(CIII).** Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen, because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load (see the What to Start section). Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see the HIV-2 Infection section.

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-3] Thus, viral load testing is an established surrogate marker for treatment response.[4] The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 $\log_{10}$ copies/mL change). Optimal viral suppression is defined as a confirmed HIV RNA level below the lower limit of detection of available assays (generally <20 copies/mL, depending on the assay used). After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression, known as a "blip," may occur in successfully treated patients and is not usually predictive of virologic failure.[5] Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.[6-9] These guidelines and the AIDS Clinical Trials Group (ACTG) now define

virologic failure as the inability to achieve or maintain suppression of viral replication to HIV RNA level <200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[10] (see the Virologic Failure section).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 12 weeks after ART initiation or after modification due to virologic failure; rarely, it may take longer in some patients. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART.** Plasma viral load should be measured before initiation of ART and within 4 to 8 weeks after treatment initiation **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII).**
- **In patients with viral suppression, with ART modification because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy **(AIII).** The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.
- **In patients on a stable, suppressive ARV regimen.** Viral load measurement should be repeated every 3 to 4 months **(AIII)** or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than a year, whose clinical and immunologic status is stable, and who are not at risk for inadequate adherence **(AIII).**
- **In patients with virologic failure who require a change in ARV regimen.** Plasma viral load should be measured before ART change and within 4 to 8 weeks after treatment modification **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to the new regimen. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII).** If viral suppression is not possible, repeat viral load measurement every 3 months or more frequently if indicated **(AIII).**
- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, several other factors—such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions—should be assessed. Patients who fail to achieve viral suppression should undergo drug-resistance testing to aid in the selection of an alternative ARV regimen (see the Drug-Resistance Testing and Virologic Failure sections).

CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in patients with HIV. It is also the strongest predictor of disease progression and survival according to findings from clinical trials and cohort studies.[11,12] CD4 counts are highly variable; a significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it **is not recommended (BIII).**

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all patients at entry into care **(AI).** It is the key factor in determining the need to initiate OI prophylaxis (see the Adult and Adolescent Opportunistic Infections Guidelines)[13] and the urgency to initiate ART **(AI)** (see the Initiation of Antiretroviral Therapy section). Although most OIs occur in patients with CD4 counts <200 cells/mm^3, some OIs can occur in patients with higher CD4 counts.[14]

Use of CD4 Count for Monitoring Therapeutic Response

The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the Adult and Adolescent Opportunistic Infections Guidelines).[13] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 cells/mm^3 to 150 cells/mm^3 in the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 cells/mm^3 to 100 cells/mm^3 per year until a steady state level is reached.[15] Patients who initiate therapy with a low CD4 count[16,17] or at an older age[18] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

ART is now recommended for all patients with HIV. In patients who remain untreated for whatever reason, CD4 counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for OI prophylaxis **(AIII).**

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII).** This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the Adult and Adolescent Opportunistic Infections Guidelines.[13] For patients beginning ART, CD4 count should be repeated every 3 months for the first 2 years of suppressive ART for those with CD4 counts <300 cells/mm^3 and every 6 months if CD4 count is ≥300 cells/mm^3. After 2 years of suppressive ART, CD4 count monitoring can be reduced to every 6 months for patients whose CD4 counts remain at <300 cells/mm^3 and every year for patients with CD4 counts between 300 cells/mm^3 and 500 cells/mm^3, and is optional for those with CD4 counts >500 cells/mm^3 **(BII).**

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution (i.e., CD4 count >500 cells/mm^3), the CD4 count provides limited information. Frequent testing is unnecessary, because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to <200 cells/mm^3 are rare in patients with viral suppression and CD4 counts >300 cells/mm^3.[19] Similarly, the ARTEMIS trial found that CD4 count monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[20] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 cells/mm^3 and 200 cells/mm^3.[21] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes, such as cardiovascular disease, malignancy, and death.[22] An analysis of costs associated with CD4 count monitoring in the United States estimated that reducing CD4 count monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately $10 million.[23]

For the patient on a suppressive ARV regimen whose CD4 count has consistently ranged between 300 cells/mm^3 and 500 cells/mm^3 for at least 2 years, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends CD4 count monitoring on an annual basis **(BII).** Continued CD4 count monitoring for virologically suppressed patients whose CD4 counts have been consistently >500 cells/mm^3 for at least 2 years may be considered optional **(CIII).** The CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a patient's clinical status that may decrease CD4 count and thus prompt OI prophylaxis. Examples of such changes include the appearance of new HIV-associated clinical symptoms or initiation of treatment known to reduce CD4 count (e.g., chronic corticosteroids, antineoplastic agents) **(AIII).** In patients who fail to maintain viral suppression while on ART, the Panel recommends CD4 count monitoring every 3 to 6 months **(AIII).**

Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications, chronic corticosteroids, or the presence of acute infections. Splenectomy[24,25] or coinfection with human T-lymphotropic virus type I (HTLV-1)[26] may cause misleadingly elevated CD4 counts. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.[27]

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care (AIII) If ART initiation is deferred, repeat before initiating ART (AIII). In patients not initiating ART, repeat testing is optional (CIII).	At entry into care (AI) If ART is deferred, every 3 to 6 months[a] (AIII)
After initiating ART	Preferably within 4 to 8 weeks after initiation of ART (AIII); thereafter, every 4 to 8 weeks until viral load is suppressed (BIII).	3 months after initiation of ART (AIII)
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen (AIII).	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 4 to 8 weeks after modification (AIII); thereafter, every 4 to 8 weeks until viral load is suppressed (BIII). If viral suppression is not possible, repeat viral load testing every 3 months or more frequently if indicated (AIII).	Every 3 to 6 months (AI)
During the first 2 years of ART	Every 3 months (AIII)	Every 3 months if CD4 <300 cells/mm^3 (BII) Every 6 months if CD4 ≥300 cells/mm^3 (BII)
After 2 years of ART (VL consistently suppressed, CD4 remains <300 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).	Every 6 months (BII)
After 2 years of ART (VL consistently suppressed, CD4 consistently 300–500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).	Every 12 months (BII)
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).	Optional (CIII)
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months (AIII) or more frequently if clinically indicated (see Virologic Failure).	Every 3 to 6 months (AIII)
Change in clinical status (e.g., new HIV clinical symptom or initiation of chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months (AIII)	Perform CD4 count and repeat as clinically indicated[b] (AIII)

[a] Some experts may repeat CD4 count measurement every 3 months in patients with low baseline CD4 counts (<200–300 cells/mm^3) before ART but every 6 months in those who initiated ART at higher CD4 counts (e.g., >300 cells/mm^3).

[b] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infection, such as new HIV-associated symptoms, or initiation of treatment with medications that are known to reduce CD4 count.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; VL = viral load

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Drug-Resistance Testing

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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).
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in ARV-naive patients (AIII).
- In people with early (acute and recent) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported (AIII).
- Standard genotypic drug-resistance testing in ARV-naive persons 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 used long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) in the past, 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 everyone with virologic failure; integrase resistance testing (which may need to be ordered separately) should be performed on individuals experiencing virologic failure while receiving an INSTI-based regimen (AII).
- For persons 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 persons who have experienced virologic failure on a regimen of long-acting CAB and rilpivirine or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation (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 for a patient (AIII).

Panel's Recommendations
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 or the gp120 attachment inhibitor fostemsavir. 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 (IAS–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 also 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 patients 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 patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses

that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with 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 with prolonged half-lives (e.g., cabotegravir [CAB] and rilpivirine [RPV]), drug pressure may persist for prolonged periods. Prospective clinical studies have shown that despite this plasma reversion, re-initiation of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and that the virus present at failure is derived from previously archived resistant virus.[15] Therefore, for persons 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 persons who have experienced virologic failure on a regimen of long-acting CAB and 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 patients 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 patients with low levels of plasma HIV RNA or in patients 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 (See Table 5 below)

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 high-risk behaviors 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 vs. 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—defined by the World Health Organization to include people exposed to ARVs prior to initiating first-line therapy (e.g., for PrEP or for the prevention of perinatal transmission)—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 can guide therapy selection to optimize virologic response in all people starting ART **(AII).** A genotypic assay is preferred for this purpose **(AIII).** In early (acute and recent) HIV infection, in pregnant people with HIV, or in people willing and able to initiate ART on the day or soon after HIV diagnosis, treatment initiation should not be delayed pending resistance testing results. Once results are reported, the regimen can be modified if warranted (see Early [Acute and Recent] HIV Infection). 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 patient 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 patients who experience virologic failure while on ART. Several prospective studies have assessed the utility of resistance testing to guide ARV drug selection in patients who experience virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6,37-43] In general, these studies found that changes in therapy based on resistance test results produced 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 patients 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 501–1,000 copies/mL**, CIII** for confirmed HIV RNA 201–500 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 it still should be considered. Conventional drug-resistance testing in people with plasma viral loads <200 copies/mL **is not recommended** because of unclear benefits and since drug-resistance assays cannot be consistently performed at very low HIV-RNA levels **(AIII).**

Resistance testing also can help to guide treatment decisions for patients with suboptimal viral load reduction **(AII).** Virologic failure in the setting of ART is, for certain patients, 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 patients who experience virologic failure or suboptimal viral load reduction while on a first or second ARV drug regimen and in patients in whom resistance mutation patterns are known or not expected to be complex (i.e., mutations that are straightforward, usually limited in number, and/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 patients with 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 patients 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. 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 patients 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 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 patients with suppressed viral load to simplify a regimen, avoid drug interactions or toxicity, or for other reasons. If a patient'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 these individuals, 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, and/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. 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 maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant people with HIV before initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV-RNA levels while on therapy **(AI).** Phenotypic testing in those found to have complex drug-resistance mutation patterns may provide additional information **(BIII).** Optimal prevention of perinatal transmission requires prompt initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

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

Clinical Setting and Recommendation	Rationale
In Early (Acute and Recent) HIV Drug-resistance testing is recommended (AII). A genotypic assay is generally preferred (AIII). Treatment should not be delayed while awaiting results of resistance testing (AIII).	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 resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AIII).	Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
Before ART Initiation in Patients 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 results of resistance testing (AIII).	Transmitted HIV with baseline resistance to at least one drug is seen in 9% to 14% of patients, and suboptimal virologic responses may be seen in patients with baseline resistance mutations to ARVs in the prescribed regimen. Some drug-resistance mutations can remain detectable for years in untreated patients with chronic HIV.
If transmitted INSTI resistance 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-lives of long-acting injectable ARV drugs, 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).	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 a patient 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 INSTIs for PrEP.
For pregnant people or if ART will be initiated 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.

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

Clinical Setting and Recommendation	Rationale
If therapy is deferred, repeat 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 patient 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.
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 Patients with Virologic Failure Drug-resistance testing is recommended in patients on combination ART with HIV-RNA levels >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 patients 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 clinician's 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 patient 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 patients must be interpreted with caution when designing subsequent ARV regimens, as mutations may decay with time.
A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second ARV regimens and for those with expected noncomplex resistance patterns (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.
All prior and current drug-resistance testing results should be reviewed and considered when designing a new ARV regimen for a patient 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.
When virologic failure occurs in a patient on an INSTI-based regimen or in a patient with a history of INSTI use, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens (AII).	Genotypic assays provide information on resistance to NRTI-, NNRTI-, PI-, and INSTI-associated mutations. In some circumstances, INSTI-resistance tests need to be ordered separately (clinicians should check with the testing laboratory).
Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns (BIII).	Phenotypic testing can provide additional useful information in patients with complex drug-resistance mutation patterns.
In Patients with Suboptimal Suppression of Viral Load Drug-resistance testing is recommended in patients 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 People with HIV Genotypic resistance testing is recommended for all pregnant people before initiation of ART (AIII) and for those entering pregnancy with detectable HIV-RNA levels while on therapy (AI).	The goals of ART in pregnant people with HIV are to achieve maximal viral suppression for treatment of maternal HIV and to prevent perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal ARV regimen for the patient. However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available, if needed.
In Patients 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 in patients with HIV RNA below the limit of detection or with low-level viremia, where a HIV-RNA genotypic assay is unlikely to be successful (CIII).	This test 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 = cabotegravir long-acting; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor; PrEP = pre-exposure prophylaxis

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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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Reviewed: January 28, 2016

Antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality at all stages of HIV infection[1-4] and has reduced HIV transmission.[5-8] Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 T lymphocyte (CD4) cell numbers, and confers substantial clinical benefits, all of which are important treatment goals.[9, 10] HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in cohorts with HIV (see Initiating Antiretroviral Therapy). Despite these benefits, eradication of HIV infection cannot be achieved with available antiretrovirals (ARVs). Treatment interruption has been associated with rebound viremia, worsening of immune function, and increased morbidity and mortality.[11] Thus, once initiated, ART should be continued, with the following key treatment goals:

- Maximally and durably suppress plasma HIV RNA;
- Restore and preserve immunologic function;
- Reduce HIV-associated morbidity and prolong the duration and quality of survival; and
- Prevent HIV transmission.

Achieving viral suppression currently requires the use of combination ARV regimens that generally include three active drugs from two or more drug classes. Baseline patient characteristics and results from drug resistance testing should guide design of the specific regimen (see What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient). When initial HIV suppression is not achieved or not maintained, changing to a new regimen with at least two active drugs is often required (see Virologic Failure).The increasing number of ARV drugs and drug classes makes viral suppression below detection limits an achievable goal in most patients.

After initiation of effective ART, viral load reduction to below limits of assay detection usually occurs within the first 12 to 24 weeks of therapy. Predictors of virologic success include the following:

- Low baseline viremia;
- High potency of the ARV regimen;
- Tolerability of the regimen;
- Convenience of the regimen; and
- Excellent adherence to the regimen.

Strategies to Achieve Treatment Goals

Selection of Initial Combination Regimen

Several ARV regimens are recommended for use in ART-naive patients (see What to Start). Most of the recommended regimens have comparable efficacy but vary in pill burden, potential for drug interactions and/or side effects, and propensity to select for resistance mutations if ART adherence is suboptimal. Regimens should be tailored for the individual patient to enhance adherence and support long-term treatment success. Considerations when selecting an ARV regimen for an individual patient include potential side effects, patient comorbidities, possible interactions with conconcomitant medications, results of pretreatment genotypic drug-resistance testing, and regimen convenience (see Table 7).

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient-related factors, such as active substance abuse, depression, or the experience of adverse effects; and health system issues, including interruptions in patient access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART (see Adherence to Antiretroviral Therapy).

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Initiation of Antiretroviral Therapy

Updated: December 18, 2019
Reviewed: December 18, 2019

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality (AI) and to prevent the transmission of HIV to others (AI). • The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV (AII). • When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

The primary goal of antiretroviral therapy (ART) is to prevent HIV-associated morbidity and mortality. This goal is accomplished by using effective ART to achieve and maintain a plasma HIV-1 RNA (viral load) below the quantification limits of commercially available assays. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS–defining complications, and allows persons with HIV to live a lifespan approaching that of persons without HIV.[1]

Another goal of ART is to reduce the risk of HIV transmission to sexual partners and to infants born to persons with HIV. High plasma HIV RNA levels are a major risk factor for HIV transmission; effective ART can reduce both viremia and the risk of transmission of HIV to sexual partners[2-6] and prevent perinatal transmission.[7, 8] Modelling studies and ecological studies of populations with high ART uptake and high viral suppression rates suggest that expanded use of ART may lower the incidence of HIV and, eventually, the prevalence of HIV on a community or population level.[9-11]

Two large, randomized controlled trials addressed the optimal time to initiate ART—START[12] and TEMPRANO.[13] Both studies demonstrated reductions in morbidity and mortality among individuals with HIV who had CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3 and who were randomized to receive ART immediately when compared to individuals who delayed initiation of ART.

Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining conditions and certain serious non-AIDS–defining conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, many individuals who start treatment with CD4 counts <350 cells/mm^3 do not achieve CD4 counts >500 cells/mm^3 after up to 10 years on ART,[14, 15] and they have a shorter life expectancy than those who initiated therapy at higher CD4 count thresholds.[14-16]

Fundamental to the recommendation for earlier initiation of ART in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. Unfortunately, in some individuals, the diagnosis of HIV is not made until the later stages of the disease. In a survey conducted between 2016 and 2017, it was noted that fewer than 40% of American adults had ever had an HIV test.[17] Evidence shows that many people with HIV access health care years before their HIV diagnosis but are not offered HIV testing despite recommendations from the Centers for Disease Control and Prevention (CDC) for routine testing for everyone aged 13 to 64 years.[18, 19] There are also economic benefits to early diagnosis, including prolonging life, improving the quality of life, and decreasing the costs related to the management of AIDS and its co-morbidities.[20, 21] Additionally, HIV screening is a key step in the Ending the HIV Epidemic initiative to prevent the transmission of HIV to others.[22]

Diagnosis of HIV is delayed more often in nonwhite individuals, those who inject drugs, those who live in rural communities, and older adults, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[23-25] Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current CDC recommendations is essential. The U.S. Preventative Services Task Force recommends HIV testing for persons aged 15 to 65 years and for all pregnant individuals. HIV testing should also be performed for younger and older persons when indicated. This recommendation has been designated a Grade A recommendation by the U.S. Preventative Services Task Force, meaning that third-party payers should cover this service without cost to patients.[26] It is critical that everyone who receives an HIV diagnosis be educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. In order for both individuals with HIV and their sexual partners to fully benefit from early diagnosis, clinicians should initiate ART as soon as possible and provide support to enhance retention in care and ART adherence (see Adherence to the Continuum of Care).

Initiating Antiretroviral Therapy

ART is recommended for all individuals with HIV to reduce the morbidity and mortality associated with HIV infection **(AI)** and to prevent HIV transmission to sexual partners and infants **(AI).** ART should be initiated as soon as possible after HIV diagnosis **(AII).** When initiating ART, it is important to educate patients about the goals and benefits of ART and to identify and address barriers to care engagement and treatment adherence **(AIII).** Patients should also understand that currently available ART does not cure HIV. To improve and maintain immunologic function and maintain viral suppression, ART should be continued indefinitely without interruption. Initiating ART early is particularly important for patients with AIDS-defining conditions, those with acute or recent HIV infection, and individuals who are pregnant; delaying therapy in these subpopulations has been associated with high risks of morbidity, mortality, and HIV transmission.

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

Since individuals may fail to engage in care between the initial HIV diagnosis (or first clinic visit) and the time ART is prescribed, some groups have proposed rapid ART initiation on the same day of HIV diagnosis as a strategy to increase ART uptake and engagement in care and to accelerate the time to ART-mediated viral suppression. Rapid ART initiation also has the potential to reduce the time during which people with newly diagnosed HIV can transmit HIV. The rapid ART initiation strategy is supported by randomized controlled trials that were performed in resource-limited settings outside of the United States[27-29] and observational trials in the United States that included both

immediate initiation of ART (on the day of diagnosis)[30-32] and rapid ART initiation (within days or weeks of diagnosis).[32, 33] The results from some of these studies are discussed below.

A randomized controlled trial conducted in South Africa enrolled 377 individuals who had recently received HIV diagnoses (median CD4 count was 210 cells/mm^3). Participants were randomized to receive ART on the day of diagnosis or to receive the usual care (three to five additional visits over 2–4 weeks before ART initiation). Those who received immediate ART were significantly more likely to be virally suppressed at 10 months (64% vs. 51% of patients achieved viral suppression, respectively).[27] In another randomized controlled trial conducted in Haiti, a higher proportion of participants who were randomized to receive same-day ART initiation were retained in care and had viral suppression at the end of 1 year than those who initiated ART at the standard time (3 weeks after HIV testing); survival was also higher in the same-day ART initiation group.[28] A novel randomized controlled trial in Lesotho compared same-day, home-based ART to usual care and standard clinic referral (which involved a minimum of two counseling sessions prior to ART initiation). Participants randomized to receive same-day ART initiation were significantly more likely to achieve linkage to care within 90 days after enrollment (68.6% vs. 43.1%) and virologic suppression at approximately 12 months (50.4% vs. 34.3%).[29]

There are many differences between health care in southern Africa and Haiti and in the United States—including differences in the health care systems, structural barriers to engagement in care, underlying HIV and tuberculosis (TB) epidemics, and ART regimens used—that limit the generalizability of the findings of the results from the studies described above. These studies, however, suggest that same-day initiation of ART is feasible and could potentially improve clinical outcomes.

While no randomized controlled trials have been conducted in the United States, several prospective observational studies have demonstrated the feasibility of same-day ART initiation. City-wide implementation of the San Francisco RAPID program among 225 patients who were newly diagnosed with HIV showed a median time from HIV diagnosis to ART start of 0 days (with a range of 0–56 days) and a median time from ART initiation to viral suppression (defined as <200 copies/mL) of 41 days. Over a median follow-up of 1.09 years (range 0–3.92 years), 92.1% of patients achieved virologic suppression. The RAPID study included a diverse and traditionally marginalized population, with a substantial proportion of participants having a major substance use disorder (51.4%), a major mental health disorder (48.1%), or unstable housing (30.6%).[31]

Whether rapid ART initiation improves long-term care engagement and virologic suppression is not yet known. One cohort study from France, however, found that earlier initiation of ART was negatively associated with care engagement at 1 year.[34] It should be emphasized that ART initiation on the same day of HIV diagnosis is resource intensive, and this strategy may require additional staff, multidisciplinary coordination, provision of ART starter packs, and consolidation of "usual care" patient services (e.g., clinical evaluation, education, counseling, initiation or optimization of insurance coverage, intake laboratory testing) into a 2- or 3-hour visit.[31] While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, removing structural barriers in order to facilitate rapid ART initiation may improve outcomes in the United States. The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends initiating ART at the time of diagnosis (when possible) or soon afterwards to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, and improve the rate of virologic suppression among individuals who have recently received HIV diagnoses **(AII).** This rating for this recommendation reflects the fact that only

observational trials have been conducted in the United States or other highly resourced countries, where health systems and socioeconomic contexts differ substantially from those in the countries where randomized trials were conducted.

Antiretroviral Therapy for Persons with Acute Opportunistic Infections and Malignancies

Initiation of ART in the setting of an acute, AIDS-associated opportunistic infection (OI) or malignancy can improve immune function and potentially enhance treatment success for the OI. Clinicians should refer to the Adult and Adolescent Opportunistic Infection Guidelines for a more in-depth discussion on specific OIs. Below is a list of important factors to consider when initiating ART in these situations.

- When no effective therapy exists for the OI (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy): In these situations, ART may be the only treatment that can improve immune function and clinical outcomes. ART should be initiated without delay in these patients (see the Adult and Adolescent Opportunistic Infection Guidelines for more information).
- Concerns regarding immune reconstitution inflammatory syndrome (IRIS): For some OIs, such as cryptococcal and TB meningitis, immediate ART initiation may increase the risk of serious IRIS. A short delay before initiating ART may be warranted.[35-38] After ART initation, the patient should be closely monitored for signs and symptoms associated with IRIS.
- Non-meningeal TB: In these patients, initiating ART during treatment for TB confers a significant survival advantage;[39-43] therefore, ART should be initiated as recommended in Tuberculosis/HIV Coinfection.
- For patients with mild to moderate cutaneous Kaposi sarcoma: Prompt initiation of ART alone without chemotherapy has been associated with improvement of cutaneous Kaposi sarcoma lesions, even though initial transient progression of Kaposi sarcoma lesions as a manifestation of IRIS can also occur.[44]
- For patients with malignancies that require chemotherapy:
    - A diagnosis of malignancy should not delay initiation of ART, nor should initiation of ART delay treatment for the malignancy.
    - Although an IRIS-like presentation of non-Hodgkin's lymphoma after initiation of ART has been described,[45] ART-mediated viral suppression is associated with longer survival among individuals undergoing treatment for AIDS-related lymphoma.[46]
    - Drug interactions should be considered when selecting ART, as there is the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some ritonavir-boosted or cobicistat-boosted regimens).

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

Randomized Controlled Trials of Early vs. Deferred Antiretroviral Therapy

Two large randomized controlled trials, START and TEMPRANO, provide the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 count **(AI).** The results of these two studies are summarized below.

START was a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART initiation in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. The study began at a time when initiating ART was not recommended until an individual's CD4 count fell below 350 cells/mm^3. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm^3 were randomized to initiate ART at randomization (early initiation arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm^3 or until they developed a clinical indication for therapy (deferred initiation arm).

The study enrolled 4,685 participants, with a mean follow-up of 3 years. The primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events per 100 person-years) who were randomized to initiate ART early, and 96 participants (4.1%, or 1.38 events per 100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART; 95% confidence interval [CI], 0.30–0.62, $P < 0.001$). The most common clinical events reported were TB and malignancies (including both AIDS and non-AIDS malignancies). The majority of clinical events (59%) in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm^3, evidence for a benefit of initiating ART even before CD4 count declines below this threshold. Furthermore, the benefit of early ART was consistent across all participant subgroups, including gender, age, plasma HIV RNA levels, and income level of country. Although START was not sufficiently powered to compare the benefits of early ART initiation and deferred ART initiation for each category of clinical events, the benefit appeared to be particularly strong for AIDS events (HR 0.28), TB (HR 0.29), malignancies (HR 0.36), and severe bacterial infections (HR 0.39). The benefit at lower CD4 counts was primarily a reduction in the number of AIDS events, while the benefit at higher CD4 counts was primarily a reduction in the number of serious non-AIDS events. Importantly, early ART initiation also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61).[12, 47]

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm3 and who did not meet the criteria for starting ART according to World Health Organization guidelines at that time were randomized to start ART early (upon enrollment) or defer ART based on the national guidelines criteria for starting treatment. Half of the participants in each group received isoniazid for prevention of TB for 6 months and half did not. The primary study endpoint was a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases.

More than 2,000 participants enrolled in the trial, with a median follow-up of 30 months. Among the 849 participants who had baseline CD4 counts >500 cells/mm^3, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower among those who were randomized to start ART early than among those in the deferred arm, with an HR of 0.56 in favor of early ART

(95% CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART initiation is beneficial in reducing the rate of these clinical events.[13]

The TEMPRANO and START trials had very similar estimates for the protective effect of ART among individuals with HIV who had CD4 counts >500 cells/mm^3, further supporting the Panel's recommendation that ART be initiated in all patients regardless of CD4 count.

Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A randomized clinical trial[3] and several large observational cohort studies[4-6] have provided strong evidence that achieving sustained viral suppression prevents sexual transmission of HIV. Thus, a key goal of ART is to prevent transmission of HIV to seronegative sexual partners **(AI).** All persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL, including any measurable value below this threshold value, with ART prevents sexual transmission of HIV to their partners **(AII).** Patients may recognize this concept as Undetectable = Untransmittable, or U=U. The results of these studies are summarized in Antiretroviral Therapy to Prevent Sexual Transmission of HIV.

Prevention of Perinatal Transmission

The first well-established example of ART reducing the risk of HIV transmission is the use of ART during pregnancy to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing the risk of perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, the use of combination ART during pregnancy has reduced the rate of perinatal HIV transmission from approximately 20% to 30% to 0.1% to 0.5%.[7, 8] ART is thus recommended for all pregnant individuals with HIV, for both maternal health and for the prevention of HIV transmission to the newborn. In ART-naive pregnant individuals, ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy. All pregnant individuals should be tested for HIV upon confirmation of pregnancy, with testing repeated throughout pregnancy as needed for those at risk of HIV acquisition (see Maternal HIV Testing and Identification of Perinatal HIV Exposure in the Perinatal Guidelines).

Considerations When Initiating Antiretroviral Therapy

The ART regimens that are currently recommended as initial therapy in these guidelines (see What to Start) can suppress and maintain viral loads below the level of quantification in most patients who adhere to their regimens. Most of the recommended regimens have a low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

Optimizing Adherence, Antiretroviral Therapy Access, and Care Engagement

The key to successfully maintaining viral suppression is continuous access to ART and adherence to the prescribed regimen. Lack of adherence or intermittent access to ART can result in treatment failure and the emergence of drug resistance mutations that may compromise future treatment options. While optimizing adherence and linkage to care and ensuring continuous access are critical regardless of the timing of ART initiation, the evidence thus far indicates that drug resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who

initiate ART earlier.[48] It is important to discuss strategies to optimize adherence, care engagement, and ART access with all patients.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, substance use disorder, unstable housing, unfavorable social circumstances, patient concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in Adherence to the Continuum of Care. However, mental illness, substance use disorder, and psychosocial challenges are not reasons to withhold ART from a patient. Rather, these issues indicate the need for additional interventions to support adherence, and they may influence the ART regimen that is recommended (see What to Start).

Considerations for Special Populations

Elite HIV Controllers

A small subset of individuals with HIV maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as elite HIV controllers.[49, 50] There are limited data on the benefits of initiating ART in these individuals. The START and TEMPRANO studies demonstrated that initiating ART is clearly beneficial for the patient regardless of CD4 count; therefore, delaying ART to see if a patient becomes an elite controller is **strongly discouraged**. Nevertheless, significant uncertainty remains about the optimal management of elite controllers who have maintained undetectable viremia in the absence of ART for years.

Given that ongoing HIV replication occurs even in elite controllers, ART is strongly recommended for controllers with evidence of HIV disease progression, which is defined by declining CD4 counts or the development of HIV-related complications **(AIII).** Nonetheless, even elite controllers with normal CD4 counts show evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS–related diseases.[49, 51-53] One observational study suggested that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[54] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[55] Whether this potential immunologic benefit of ART in elite controllers outweighs the potential risks of ART toxicity and results in clinical benefit is unclear. Unfortunately, it is unlikely that randomized controlled trials will be able to address this question, given the very low prevalence of elite controllers. Although the START study included a number of participants with very low viral loads and demonstrated the benefit of immediate ART initiation regardless of the extent of viremia, the study did not include a sufficient number of controllers to definitively determine the clinical impact of ART in this specific population.[56] Nevertheless, there is a clear rationale for prescribing ART to elite controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.

Adolescents with HIV

Neither the START trial nor the TEMPRANO trial included adolescents. The Panel's recommendation to initiate ART in all patients is extrapolated to adolescents based on the expectation that they will derive benefits from early ART initiation that are similar to those observed in adults. Compared to adults, youth have demonstrated significantly lower levels of ART adherence and viral suppression, and higher rates of viral rebound following initial viral suppression.[57] In recent years, more adolescents have been prescribed once-daily regimens, which has increased the rate of viral suppression in this population, even though there has been no significant difference in treatment adherence.[58] Because youth often face psychosocial and other barriers to adherence, their ability to adhere to therapy should be carefully considered when making decisions about ART initiation. Although some adolescents may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to receiving care and to adherence. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support to adolescent patients (see Adolescents and Young Adults with HIV).[59]

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Antiretroviral Therapy to Prevent Sexual Transmission of HIV (Treatment as Prevention)

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Panel's Recommendations
• All persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL, including any measurable value below this threshold value, with antiretroviral therapy (ART) prevents sexual transmission of HIV to their partners. Patients may recognize this concept as Undetectable = Untransmittable or U=U (AII). • Persons with HIV who are starting ART should use another form of prevention with sexual partners (e.g., condoms, pre-exposure prophylaxis [PrEP] for the HIV-negative sexual partner, sexual abstinence) for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented (AII). Many experts would recommend confirming sustained suppression before assuming that there is no further risk of sexual HIV transmission (AIII). • When the viral load is ≥200 copies/mL, additional methods are needed to prevent transmission of HIV to sexual partners until resuppression to <200 copies/mL has been confirmed (AIII). • Persons with HIV who intend to rely upon ART for prevention need to maintain high levels of ART adherence (AIII). They should be informed that transmission is possible during periods of poor adherence or treatment interruption (AIII). • At each visit for HIV care, clinicians should assess adherence to ART and counsel patients regarding the importance of ART to their own health as well as its role in preventing sexual HIV transmission (AIII). • Providers should inform patients that maintaining a viral load of <200 copies/mL does not prevent acquisition or transmission of other sexually transmitted infections (STIs) (AII). • Providers should also routinely screen all sexually active persons with HIV for STIs, both for their own health and to prevent transmission of STIs to others (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral therapy (ART) not only reduces morbidity and mortality for persons with HIV but has now been definitively shown to prevent sexual transmission of the virus when the plasma HIV RNA (viral load) is consistently suppressed to <200 copies/mL, which includes any measurable viral load that is lower than this threshold value. Providers who manage patients with HIV need to be aware of the data supporting treatment as prevention (TasP, which persons with HIV may recognize as Undetectable = Untransmittable or U=U), its implications, and how to operationalize this prevention strategy in clinical practice. For persons with HIV who intend to rely on TasP for HIV prevention, providers should make an individualized assessment of the person's risk tolerance, personal health, history of maintaining viral suppression on treatment, and access to health care services and ART, as well as other factors that may affect their ability to maintain a high level of adherence to ART.

Evidence That Viral Load Suppression Prevents Sexual HIV Transmission

Suppressing the HIV viral load to <200 copies/mL with ART prevents sexual transmission of HIV. Observational data collected in the early 1990s from heterosexual couples demonstrated that sexual transmission from untreated persons with HIV was rare at viral loads of <1,000 copies/mL to 1,500 copies/mL and that the risk of transmission increased in dose-response fashion with increasing viral

load.[1, 2] Additional reports[3-7] and a meta-analysis[8] supported the observation that sexual HIV transmission risk in heterosexual persons was correlated with plasma viral load, and transmission was infrequent below the lowest limits of quantification for the viral load assays used at the time.

The first prospective clinical trial designed specifically to address this question was HPTN 052, which randomized people with HIV who were in mixed HIV status couples (previously referred to as serodiscordant couples) to initiate ART early or to delay initiation. Initial results from this study were reported in 2011,[9] with final results reported in 2016.[10] The 2016 analysis reported that no phylogenetically linked sexual transmissions of HIV occurred among 1,763 couples who were followed a median of 5.5 years while the person with HIV was on ART and had a viral load <400 copies/mL for at least 6 months. Notably, four phylogenetically linked infections occurred within the 90 days after the partner with HIV had started ART and was presumably not yet virally suppressed, and four others occurred after the partner with HIV had experienced virologic failure. There were also a number of transmission events that were not phylogenetically linked, indicating acquisition from someone other than the enrolled study index partner.[11] HPTN 052 was conducted almost exclusively among heterosexual couples that lived in Africa and Asia and did not track the number or type of sexual exposures. In addition, ART was used as an adjunct to a comprehensive prevention package that provided condoms and encouraged condom use, as well as frequent testing for HIV and other sexually transmitted infections (STIs).

Three prospective observational studies—PARTNER 1,[12] PARTNER 2,[13] and Opposites Attract[14]—provided data from more diverse populations of mixed HIV status couples in which condomless sex was common. Clinical follow-up in these studies closely mimicked that of routine clinical care. Conducted in 14 European countries (PARTNER 1 and PARTNER 2) as well as Australia, Thailand, and Brazil (Opposites Attract), the investigators followed 548 heterosexual and 1,481 male-male mixed HIV status couples that engaged in 144,631 episodes of condomless vaginal or anal sex while the partner with HIV had a suppressed viral load on ART, defined as <200 copies/mL. In these studies, no phylogenetically linked transmissions were observed; however, as in HPTN 052, there were numerous non-phylogenetically linked transmissions attributed to partners outside the enrolled study couple relationship.

Integrating the Principles of Treatment as Prevention into Clinical Care

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that providers inform all persons with HIV that maintaining an HIV viral load <200 copies/mL with ART prevents sexual transmission of HIV **(AII).** This information may help motivate patients and help relieve stigma that can be a barrier to getting tested and entering into care, starting and remaining adherent to ART, and ultimately achieving and maintaining a viral load <200 copies/mL.[15] Although PARTNER 1, PARTNER 2, and Opposites Attract were designed to follow patients in the study as they would be typically be followed in clinical care for HIV, the participants reported high levels of ART adherence at study entry and many reported at least 1 year of condomless sex with an established sexual partner without transmission. As the principles of TasP are integrated into the clinical management of people with HIV who are on ART, implementation research will be critical to maximize the effectiveness of TasP in practice.

Frequency of Viral Load Assessment

The Panel has issued recommendations for viral load monitoring to manage the health of persons with HIV (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring). However, current data

are insufficient to determine whether these recommendations represent the optimal monitoring schedule for the purpose of preventing sexual transmission of HIV. In the PARTNER studies and Opposites Attract, viral loads were generally assessed every 3 to 6 months during study follow-up, usually during the course of regular HIV care. Pending further data, the Panel recommends no change to the existing recommendations for monitoring viral load (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring) **(BII).**

Time to Adequate Suppression after Starting Antiretroviral Therapy

A subgroup analysis from the Partners PrEP Study provided data regarding the risk of HIV transmission during and after the first 6 months on ART for the partner with HIV.[16] This analysis included 1,573 heterosexual East African couples in which the partners without HIV were randomized to the placebo arm of the Partners PrEP Study and were tested monthly for HIV while the viral load of the partner with HIV was assessed every 6 months. Three phylogenetically linked infections were diagnosed in the 6 months prior to the first follow-up visit for the partners with HIV. The observed incidence rate of 1.79 per 100 person-years during this initial 6-month period after the partner with HIV started ART was slightly less than the 2.08 per person-years incidence rate observed in couples in which the person with HIV was not receiving ART. Viral suppression in this study was defined as <40 copies/mL, and the three infections were diagnosed at 0 days, 56 days, and 149 days after the partner with HIV started ART. After the partners with HIV had been taking ART for ≥6 months, no further transmissions were observed.

At this time, the Panel recommends that persons with HIV who are starting ART use another form of prevention with sexual partners for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented **(AII).** Many experts would recommend confirming sustained suppression before assuming that there is no further risk of sexual transmission of HIV **(AIII).**

Adherence to Antiretroviral Therapy

Adherence to ART is paramount for persons who intend to prevent HIV transmission by achieving and maintaining a suppressed viral load. Viral rebound typically occurs within days to weeks after ART cessation and has been observed as early as 3 to 6 days after stopping treatment.[17-29] The minimum level of adherence that is required to prevent sexual transmission has not been determined and may vary depending on the ART regimen. In the key studies that defined the efficacy of TasP, adherence levels prior to study entry and during follow-up were very high. In clinical practice, most people who start ART will achieve a viral load <200 copies/mL within 6 months, but once this viral load is achieved, maintaining viral suppression can be a challenge, especially for those who have difficulty accessing ART and other HIV care. The Centers for Disease Control and Prevention (CDC) estimates that during 2015, 60% of persons with HIV and 78% of persons engaged in clinical care had viral loads <200 copies/mL at their most recent assessment.[30] Observational cohort data have demonstrated that within the first year of starting ART, up to 10% of persons with HIV can experience loss of viral suppression; however, the likelihood of maintaining a suppressed viral load generally improves over time. After a few years, 5% or fewer of persons on ART may experience loss of viral suppression.[31, 32]

The Panel recommends that persons with HIV who intend to rely upon TasP be made aware of the need for high levels of ART adherence **(AIII).** The Panel further recommends that adherence be assessed and counseling be provided at each visit for HIV care to reinforce the importance of adherence for the individual's health as well as its role in preventing HIV transmission **(AIII).**

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

Adherence can be especially challenging for certain groups of patients, such as adolescents and young adults, homeless persons, persons with active substance use disorder, and persons who are involved with the criminal justice system. Recommendations to help manage and maximize ART adherence can be found in Adherence to the Continuum of Care. Persons for whom there is concern about adherence also merit counseling on how to properly use other prevention methods, especially barrier methods that prevent STIs.

Managing Transient Viremia, or "Blips"

Highly adherent patients may experience intermittent or transient viremia, commonly termed "viral blips." Blips are defined in the context of effective treatment as a single, measurable HIV RNA level, typically <200 copies/mL, that is followed by a return to a viral load below the limit of detection or quantification. With contemporary ART regimens, about 10% of persons per year who are adherent to ART may experience a blip.[33-35] Most blips likely represent normal biological fluctuation (i.e., variation around a mean undetectable viral load) or laboratory artifact and not inadequate adherence.[36-38] Persistent viremia ≥200 copies/mL has been associated with increasing risk of virologic failure[33, 39] that, in the context of TasP, can lead to increased risk of sexual transmission.[10] The PARTNER studies and Opposites Attract excluded observation time when the viral load of the participant with HIV was ≥200 copies/mL. The frequency of blips <200 copies/mL was not reported in Opposites Attract; however, in PARTNER 1 and PARTNER 2, transient elevations in viral loads above the limit of detection (50 copies/mL in these studies) but <200 copies/ml were observed for 6% and 4% of the total follow-up time, respectively, during which time no phylogenetically linked infections were observed.

One of the clinical challenges with blips is that they can only be defined retrospectively once the viral load has returned to a suppressed value. The Panel recommends that when the viral load is ≥200 copies/mL, persons with HIV and their sexual partners should use another form of prevention (e.g., condoms, pre-exposure prophylaxis for sexual partners without HIV, sexual abstinence) to protect against HIV transmission until a viral load <200 copies/mL is achieved (AII). This recommendation applies both to persons who are starting ART (as noted earlier) and to those who have been taking ART and have achieved viral suppression but develop viral loads ≥200 copies/mL.

In cases where a patient achieves resuppression to <200 copies/mL after a detectable viral load ≥200 copies/mL, or when a patient with a viral load <200 copies/mL switches regimens (e.g., for regimen simplification or to avoid certain side effects), providers should check the viral load per recommendations in Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression, respectively **(AIII).** There are presently no data to guide how long, if at all, a person might need to continue to use another form of prevention in these two circumstances. Individualized assessment is recommended based on the length and quality of adherence and time with viral load <200 copies/mL preceding the viral load ≥200 copies/mL.

Effect of Sexually Transmitted Infections on Treatment as Prevention

The presence of STIs in a person with HIV does not appear to meaningfully alter the risk of sexual transmission when the person's viral load is <200 copies/mL. The PARTNER studies and the

Opposites Attract study regularly assessed participants for STIs, which were diagnosed in 6% of heterosexual participants and 13% to 27% of men who have sex with men. Although the authors of the studies noted that their findings could not rule out the possibility that STIs in participants with viral loads <200 copies/mL might affect the risk of HIV transmission, when viewed collectively, these data suggest that any effect is very small, since STIs were common and no linked infections were observed. The Panel recommends that patients using TasP be informed that maintaining a viral load of <200 copies/mL does not prevent acquisition or transmission of other STIs, and that it is not substitute for condoms or behavioral modifications **(AII).** Providers should also routinely screen all sexually active persons with HIV for STIs, both for their own health and to prevent transmission of STIs to others **(AIII).** Refer to CDC's Sexually Transmitted Diseases Treatment Guidelines for details.

Treatment as Prevention Applies Only to Sexual Transmission of HIV

Available clinical data only support the use of TasP to prevent sexual HIV transmission in patients with viral loads <200 copies/mL. The effectiveness of this strategy to prevent transmission from blood exposure (e.g., through nonsterile drug injection) has not been determined. In addition, while suppression of maternal viral load substantially reduces the risk of perinatal transmission and transmission through breastfeeding, it does not eliminate these risks, and transmission has occurred via breastfeeding despite continuous viral suppression (refer to the Perinatal Guidelines for details).

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What to Start: Initial Combination Antiretroviral Regimens for People with HIV

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Key Considerations and Recommendations

- An initial antiretroviral (ARV) regimen for a person with HIV generally consists of two nucleoside reverse transcriptase inhibitors administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).
- Data also support the use of the two-drug regimen, dolutegravir (DTG) plus lamivudine (3TC), for initial treatment.
- Before initiating antiretroviral therapy (ART) in a person of childbearing potential, clinicians should discuss the person's intentions regarding pregnancy and a pregnancy test should be performed (AIII). Clinicians should refer to the Perinatal Guidelines for recommendations on initial ARV treatment around the time of conception and during pregnancy.
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the regimens below (in alphabetical order) as *Recommended Initial Regimens for Most People with HIV*.

  For people with HIV who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), the following regimens are recommended:

  - Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC) (AI)[a]
  - DTG/abacavir/3TC—only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection (AI)
  - DTG plus (TAF or tenofovir disoproxil fumarate [TDF])[b] plus (FTC or 3TC) (AI)
  - DTG/3TC (AI)—except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

  For people with HIV and a history of using CAB-LA as PrEP, INSTI genotypic resistance testing should be done before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:

  - Boosted darunavir plus (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test (AIII).
- To address individual patient characteristics and needs, the Panel also provides a list of *Recommended Initial Regimens in Certain Clinical Situations* (see Table 6 below).
- Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance-test results, comorbid conditions, access, and cost. For guidance on choosing an ARV regimen based on selected clinical case scenarios, see Table 7. Also see Table 9 for the advantages and disadvantages of different components in an ARV regimen.
- Patients without prior ART use who wish to begin long-acting intramuscular CAB and rilpivirine (RPV) should first achieve viral suppression on another regimen before switching to CAB and RPV (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression).

Key Considerations and Recommendations
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] Bictegravir should not be initiated in pregnant people due to insufficient data in pregnancy.

[b] TAF and TDF are two forms of tenofovir that are 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.

Introduction

More than 30 antiretroviral (ARV) drugs in eight mechanistic classes are U.S. Food and Drug Administration (FDA)-approved for treatment of HIV infection. These eight classes are nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, a CD4 T lymphocyte (CD4) post-attachment inhibitor, and a gp120 attachment inhibitor. In addition, two drugs, ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of PIs and the INSTI elvitegravir (EVG).

The initial ARV treatment regimen for a person with HIV generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy for initial treatment has resulted in suppression of HIV replication and CD4 count increases in most people with HIV.[1-3] Additional data now support the use of the two-drug regimen dolutegravir/lamivudine (DTG/3TC) for initial treatment of some people with HIV.[4]

Supporting Evidence and Rationale Used for the Panel's Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents' (the Panel) 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 show no significant differences in HIV-related clinical endpoints (such as progression to AIDS-defining conditions) or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (i.e., rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include ARV drugs approved by the FDA based on bioequivalence or relative bioavailability studies that demonstrate that the exposure of the drug(s) in the new formulation or combination is comparable to the exposure of a reference drug(s)

that has demonstrated safety and efficacy in randomized clinical trials. When developing recommendations, the Panel may also consider data from randomized switch studies in which a drug in an ARV initial regimen that suppressed patients' viral loads is replaced by a new drug from the same class. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they only examine the drug or regimen's ability to maintain suppression. Therefore, results from switch trials may not be directly applicable to the selection of an initial regimen and should be considered in conjunction with other data, including data from bioavailability/bioequivalence studies and from trials conducted in people taking their first ARV treatment regimen. In this section of the guidelines, the definition of an evidence rating of **II** is expanded to include supporting data from bioavailability/bioequivalence studies or randomized switch studies.

When developing recommendations, the Panel also considers tolerability and toxicity profiles, pill burden and dosing frequency, drug interaction potential, cost and access, post-marketing 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* and (2) *Recommended Initial Regimens in Certain Clinical Situations* (see Table 6 below). *Recommended Initial Regimens for Most People with HIV* are those regimens with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. The Panel also recognizes that, in certain clinical situations, other regimens may be preferred; these options are included in Table 6 in the category of *Recommended Initial Regimens in Certain Clinical Situations*. See Table 7 for examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous.

There are many other ARV regimens that are effective for initial therapy but have disadvantages when compared with the regimens listed in Table 6. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, or limitations for use in certain patient populations. These regimens are no longer included in Table 6. A person with HIV who has a suppressed viral load and is not experiencing any adverse effects while on a regimen that is not listed in Table 6 need not necessarily change to one that is listed in the table. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.

The ARV drugs and regimens listed in Table 10 are not recommended as initial therapy. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 10 to a recommended regimen.

In addition to these tables, several tables in these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 3–9 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 11 provides ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Changes Since the Last Revision of the Guidelines

Since the last revision of these guidelines, the Panel has made several important changes to the recommendations for initial therapy in people with HIV. Among these changes, the following deserve emphasis:

- Long-acting injectable cabotegravir (CAB-LA) was approved by the FDA for HIV pre-exposure prophylaxis (PrEP). Because of the long half-life of CAB-LA, drug levels may be present in some individuals for up to 4 years. This persistent drug exposure at levels suboptimal to prevent infection may select for INSTI-resistant virus. Therefore, in this setting, the Panel recommends that results of an INSTI genotypic resistance test be available before initiating an INSTI-based regimen, because the presence of cabotegravir (CAB)-resistant mutations may have cross-resistance to other INSTIs, including bictegravir (BIC) and dolutegravir (DTG). When antiretroviral therapy (ART) is initiated before an INSTI genotype result is available, a non-INSTI regimen containing boosted darunavir (DRV) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF]) plus (emtricitabine [FTC] or lamivudine [3TC]) should be initiated, pending genotype results. If an INSTI-based regimen is initiated and viral suppression is not achieved, genotypic resistance testing (including for INSTIs) should be repeated.

Table 6. Recommended Antiretroviral Regimens for Initial Therapy

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, childbearing potential and use of effective contraception, pill burden, dosing frequency, drug–drug interaction potential, comorbid conditions, cost, access, and resistance-test results. A pregnancy test should be performed in persons of childbearing potential, and choice of ART for pregnant individuals should be guided by recommendations from the Perinatal Guidelines. Drug classes and regimens within each class are arranged first by evidence rating and, when ratings are equal, in alphabetical order. See Table 7 for ARV recommendations based on specific clinical scenarios.

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 CAB-LA use as PrEP, the following regimens are recommended: INSTI plus Two NRTIs • BIC/TAF/FTC (AI)[a] • DTG/ABC/3TC (AI)—if HLA-B*5701 negative • DTG plus (TAF or TDF)[c] plus (FTC or 3TC) (AI) INSTI plus One NRTI • DTG/3TC (AI), except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available *For people with HIV and a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:* • DRV/c[b] or DRV/r with (TAF or TDF)[c] plus (FTC or 3TC)—pending the results of the genotype test (AIII)

Table 6. Recommended Antiretroviral Regimens for Initial Therapy

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have fewer supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus Two NRTIs

- EVG/c/(TAF or TDF)[c] FTC (BI)[b]
- RAL plus (TAF or TDF)[c] plus (FTC or 3TC) (BI for TDF/[FTC or 3TC], BII for TAF/FTC)

Boosted PI plus Two NRTIs

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c[b] or DRV/r) plus (TAF or TDF)[c] plus (FTC or 3TC) (AI)[b]
- (ATV/c[b] or ATV/r) plus (TAF or TDF)[c] plus (FTC or 3TC) (BI)[b]
- (DRV/c[b] or DRV/r) plus ABC/3TC—if HLA-B*5701 negative (BII)[b]

NNRTI plus Two NRTIs

- DOR/TDF[c]/3TC (BI) or DOR plus TAF[c]/FTC (BIII)
- EFV plus (TAF or TDF)[c] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) (BI)
  - EFV 400 mg/TDF/3TC (BI)
  - EFV 600 mg plus TAF/FTC (BII)
- RPV/(TAF or TDF)[c]/FTC (BII for TAF and BI for TDF)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3

Regimens to Consider When ABC, TAF, and TDF Cannot Be Used or Are Not Optimal

- DTG/3TC (AI), except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day (CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3
- DRV/r once daily plus 3TC (CI)

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] BIC should not be initiated in pregnant people due to insufficient data.

[b] COBI should be avoided in pregnancy because lower concentrations of COBI and its boosted drugs—EVG, DRV, and ATV—have been observed during the second and third trimesters. For individuals with viral suppression who become pregnant while on a COBI-containing regimen and wish to remain on that regimen after counseling regarding lower drug concentration, frequent viral load monitoring is recommended. For further information, refer to the Perinatal Guidelines.

[c] TAF and TDF are two forms of TFV approved by the FDA. 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.

Table 6. Recommended Antiretroviral Regimens for Initial Therapy

Note: The following are available as coformulated drugs: ABC/3TC, ATV/c, BIC/TAF/FTC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/3TC, DTG/ABC/3TC, EFV (400 mg or 600 mg)/TDF/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB-LA = cabotegravir long-acting; CD4 = CD4 T lymphocyte; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; 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; PrEP = pre-exposure prophylaxis; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Selecting an Initial Antiretroviral Regimen

The goal of ART is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen in order to achieve sustained virologic control. Initial therapy should be with two NRTIs combined with an INSTI, the combination of DTG/3TC or, in some individuals, a combination including two NRTIs plus an NNRTI or an RTV- or COBI-boosted PI. When selecting a regimen for a person with HIV, a number of patient- and regimen-specific characteristics should be considered. Some of the factors can be grouped into the categories listed below, and these factors may influence the selection of a regimen. See Table 7 for additional regimen recommendations to use in specific clinical scenarios. Individuals without prior ART treatment who wish to use long-acting injectable CAB and rilpivirine (RPV) should first achieve viral suppression on another regimen before shifting to oral, and then injectable, CAB and RPV (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression).

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 as PrEP
- HIV genotypic drug resistance test results. Based on current rates of transmitted drug resistance to different ARV drugs, standard genotypic drug resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase and protease genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs. People who acquired HIV after a history of taking CAB-LA as PrEP should have a blood specimen collected for INSTI genotypic resistance testing prior to ART initiation, but they may initiate non–INSTI-based ART prior to receipt of results.
- HLA-B*5701 status. Those who are HLA-B*5701 positive should not receive ABC. Regimens that do not include ABC can be initiated if HLA-B*5701 test results are not yet available; see Table 7 for regimens to initiate.
- Individual preferences
- Anticipated adherence to the regimen
- Whether ART initiation occurs prior to availability of baseline laboratory results

- It should be noted that results of pre-treatment HIV RNA, CD4 count, and resistance testing do not need to be available before starting ART, unless the individual is planning to begin an INSTI-containing regimen and has had prior exposure to CAB-LA as PrEP. See Table 7 for regimens to initiate if these results are not available.

Presence of Specific Conditions

- Comorbid conditions: Cardiovascular disease; hyperlipidemia; renal disease; liver disease; osteopenia, osteoporosis, or other conditions associated with bone mineral density loss; psychiatric illness; neurologic disease; substance use disorder requiring narcotic replacement therapy
- Coinfections: Hepatitis B virus (HBV), hepatitis C virus, tuberculosis (TB)
- Pregnancy and potential for pregnancy: See below, General Considerations for Persons of Childbearing Potential Initiating Antiretroviral Therapy

Regimen-Specific Considerations

- Regimen's barrier to resistance
- Potential adverse effects and drug toxicities, including risk for development of comorbid diseases
- Known or potential drug interactions with other medications (see Drug–Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of a fixed-dose combination or single-tablet regimen [STR] formulations, food requirements)
- Cost and access (see Cost Considerations and Antiretroviral Therapy)

General Considerations for Persons of Childbearing Potential Initiating Antiretroviral Therapy

- A pregnancy test should be performed before initiating ART.
- Clinicians should discuss intentions regarding pregnancy with all persons of childbearing potential.
- People with HIV should attain maximum viral suppression before attempting conception in order to protect their own health, prevent sexual HIV transmission to partners without HIV, and minimize the risk of perinatal HIV transmission to the infant.
- A DTG-based regimen is one of the recommended options for persons of childbearing potential initiating ART. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision. Please refer to the Women with HIV section and INSTI-Based Regimens below for additional details.
- 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

The choice between an INSTI, PI, or NNRTI in an initial ARV regimen should be guided by the ARV drug's efficacy, barrier to resistance, and adverse effects profile; convenience; the patient's comorbidities and concomitant medications; the potential for drug–drug interactions (see Tables 7 and 9); and whether the individual has been exposed to CAB-LA as PrEP prior to HIV acquisition.

Due to concerns about INSTI resistance in the setting of past use of CAB-LA as PrEP, the Panel recommends initiating a boosted PI regimen of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) plus (TAF or TDF) plus (FTC or 3TC) while awaiting availability of INSTI genotype results. In HPTN 083, a study of CAB-LA as PrEP in cisgender men and transgender women, CAB-resistant mutations were reported in one of four cases of persons who received CAB-LA but had undetected HIV infection at baseline and in four of nine cases of incident HIV infection. In this study, there were no cases of infection during the tail phase of CAB decay following the last dose.[5] One additional HIV acquisition with INSTI-resistant mutations occurred during the oral CAB lead-in phase.[6] In HPTN 084, a study of CAB-LA as PrEP in cisgender women, four HIV infections occurred in the CAB-LA arm (one baseline, three incident) and no CAB-resistant mutations were detected. All individuals had low or unquantifiable CAB levels. Two of the three persons with incident infection never received injectable CAB.[7] HPTN 077, a PK study of CAB-LA, suggested that suboptimal CAB levels could persist for as long as 3 years in men and 4 years in women, suggesting that HIV acquisition following even distant CAB-LA exposure may confer risk of INSTI resistance.[8]

INSTI-Based Regimens

The Panel's *Recommended Initial Regimens for Most People with HIV* as listed in Table 6 include one of two INSTIs (BIC or DTG) plus two NRTIs or DTG/3TC for persons 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 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 patients, these INSTI-containing regimens will be highly effective and have relatively infrequent treatment-limiting adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations.[9-11] The Panel recommends a two-drug regimen of DTG/3TC for initial therapy if certain criteria are met. Data from two randomized trials showed that, in terms of virologic efficacy, DTG plus 3TC was noninferior to a three-drug regimen of DTG plus TDF/FTC. No treatment-emergent resistance was seen in either the two-drug or the three-drug group. The study inclusion criteria limited enrollment to participants with HIV RNA levels <500,000 copies/mL; no known major NRTI, PI, or NNRTI resistance; and without active HBV.[4,12]

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance and lower pill burden than the first-generation INSTI-based regimens that contain EVG or raltegravir (RAL). Treatment-emergent resistance has been reported very rarely in individuals receiving three-drug DTG-based therapy[13-15] and rarely has been reported in those receiving BIC-based regimens.[16] In addition, transmitted resistance to BIC and DTG is rare. Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens may be considered for

patients who plan to start ART before resistance-test 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.[17,18]

Preliminary data from a birth outcomes surveillance study in Botswana suggested an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[19] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[20] For persons of childbearing potential who are trying to conceive, DTG-based regimens are among the recommended options for most individuals initiating ART, but clinicians should discuss the risks and benefits of using DTG in persons of childbearing potential to allow them to make an informed decision. BIC/TAF/FTC should not be used in pregnant people due to insufficient data in pregnancy. Because of inadequate drug levels in the second and third trimesters of pregnancy, COBI-boosted EVG should be avoided in a pregnant person. People with suppressed virus on a COBI-boosted regimen who wish to continue the regimen should be followed with frequent viral load monitoring. TAF is now recommended by the Perinatal Guidelines as an alternate drug in pregnancy due to insufficient data on teratogenicity in humans but reassuring data from the Antiretroviral Pregnancy Registry. Clinicians should refer to the Perinatal Guidelines before prescribing ART to a pregnant person or a person of childbearing potential.

There are now data suggesting greater weight gain with certain INSTI-based regimens and TAF than with other ARV drugs. The clinical significance of these findings is still unknown.[21-27]

EVG- and RAL-based regimens have the disadvantage of having lower barriers to resistance than DTG- or BIC-containing regimens and, therefore, are not recommended regimens for most people with HIV. Also of importance is that EVG-based regimens have a greater potential for drug interactions, because EVG is combined with COBI (EVG/c), a strong cytochrome P 3A4 inhibitor (see Table 7).

PI-Based Regimens

PK-enhanced PI-based regimens also are recommended in certain clinical situations. Similar to EVG/c, they have the disadvantage of greater drug interaction potential than other ARV drugs. For those individuals in whom ART needs to begin urgently before resistance-test results are available, boosted DRV may be an appropriate choice because the rate of transmitted PI resistance is low, and boosted DRV has a high barrier to resistance and a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is available as an STR. Boosted atazanavir (ATV), like boosted DRV, has relatively few metabolic adverse effects in comparison to older boosted-PI regimens; however, atazanavir/ritonavir (ATV/r) had a higher rate of adverse effect-associated drug discontinuation than DRV/r or RAL in a randomized clinical trial.[9] In a substudy of this trial, and in a separate cohort study, ATV/r use was associated with slower progression of atherosclerosis, as measured by carotid artery intima medial thickness.[28,29] Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir, indinavir, and RTV-boosted lopinavir) and an increased risk of cardiovascular events; however, this association was not seen with ATV.[30-35] Further study is needed. DRV/c and COBI-boosted ATV should be avoided during pregnancy because of inadequate drug levels.

NNRTI-Based Regimens

NNRTI-based regimens (which include doravirine [DOR], efavirenz [EFV], or RPV plus 2-NRTIs) may be options for some patients, although these drugs, especially EFV and RPV, have low barriers to resistance. The emergence of resistance at the time of virologic failure also has been reported with DOR. EFV has a long track record of widespread use, is considered safe in persons of childbearing potential, and has minimal PK interaction with rifamycins, making it an attractive option for patients who require TB treatment. EFV-based regimens (using either 400-mg or 600-mg dosing) have excellent virologic efficacy,[36] including in patients with high HIV RNA (except when EFV is used with ABC/3TC). However, the relatively high rate of central nervous system (CNS)-related side effects reduces the tolerability of EFV-based regimens. As an STR, EFV 600 mg is available with TDF/FTC or TDF/3TC; EFV 400 mg is available with TDF/3TC. RPV has fewer adverse effects than EFV, is available as one of the smallest tablet sizes among STRs that also include TAF/FTC or TDF/FTC, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with baseline HIV RNA levels >100,000 copies/mL and CD4 counts <200 cells/mm^3. 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 EFV and DRV/r when either of these drugs were taken in combination with two NRTIs.[37,38] DOR has CNS tolerability advantages over EFV and more favorable lipid effects than 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 patients with high HIV RNA levels and low CD4 counts. In a cross-trial analysis, DOR was not associated with weight gain compared with EFV 600 mg or boosted DRV.[39]

Regimens When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

In those patients in whom ABC, TDF, or TAF cannot be used or are not optimal, there are several two-drug options that do not contain these agents. Two-drug ARV options **should not be used** in individuals with HBV coinfection (unless separate HBV treatment is also used) or in those with known pre-existing resistance to any of the ARVs in the combination. Among the two-drug regimens, DTG/3TC is preferred because there are substantial data for this combination in initial therapy, with the caveat that people with HIV RNA >500,000 copies/mL were excluded from the largest trial.[4,12] Another two-drug treatment option that can be considered is the combination of DRV/r (once daily) plus RAL (twice daily), but this combination should only be used in those with baseline CD4 counts >200 cells/mm^3 and HIV RNA levels <100,000 copies/mL.[40] A small randomized trial indicated that once-daily DRV/r plus 3TC had similar efficacy to once-daily DRV/r plus TDF/3TC, although this study has yet to be published.[41]

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

Updated: September 21, 2022
Reviewed: September 21, 2022

This table guides clinicians in choosing an initial antiretroviral (ARV) regimen according to various patient and regimen characteristics and specific clinical scenarios. 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. This table is intended to guide the choice of an initial regimen. However, if a person is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see Table 9 for additional information regarding the advantages and disadvantages of particular ARV medications.

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/mm^3	Do Not Use the Following Regimens: • RPV-based regimens • DRV/r plus RAL	A higher rate of virologic failure has been observed in those with low pre-treatment CD4 counts.
	HIV RNA >100,000 copies/mL (also see next row if HIV RNA >500,000 copies/mL)	Do Not Use the Following Regimens: • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virologic failure have been observed in those with high pre-treatment HIV RNA levels.
	HIV RNA >500,000 copies/mL	Do Not Use the Following Regimens: • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL • DTG/3TC	For DTG/3TC, limited data are available in patients with viral loads above this threshold.
	HLA-B*5701 positive or result unknown	Do not use ABC-containing regimens.	ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.
	Prior exposure to CAB-LA PrEP.	Avoid INSTI-based regimens, unless an INSTI genotype shows no resistance mutations.	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

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Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
		Recommended Regimen Pending INSTI Genotype Results • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC)	infection and may select for resistant virus.
	An ARV regimen should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly.	Avoid NNRTI-based regimens and DTG/3TC. Avoid ABC. Recommended ARV Regimens in Persons Without Exposure to CAB-LA PrEP • BIC/TAF/FTC • DTG plus (TAF or TDF)[a] plus (3TC or FTC) • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC) Recommended ARV Regimen in Persons on CAB-LA PrEP Prior to HIV Acquisition • (DRV/r or DRV/c) 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. Transmitted resistance to DRV, BIC, and DTG is rare, and these drugs have high barriers to resistance. 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 resistant virus.
ART-Specific Characteristics	A one-pill, once-daily regimen is desired.	STR Options as Initial ART Include the Following: • BIC/TAF/FTC • DOR/TDF/3TC • DRV/c/TAF/FTC • DTG/ABC/3TC • DTG/3TC • EFV/TDF/FTC • EFV/TDF/3TC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use DTG/ABC/3TC if the patient is HLA-B*5701 positive. DTG/3TC is not recommended if HIV RNA is >500,000 copies/mL. Do not use DTG/ABC/3TC or DTG/3TC in the setting of HBV coinfection or unknown HBV status. Do not use RPV-based regimens if HIV RNA is >100,000 copies/mL and CD4 count is <200 cells/mm^3. See Appendix B, Table 11 for ARV dose recommendations in the setting of renal impairment.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Food effects	Regimens That Can Be Taken Without Regard to Food • BIC-, DOR-, DTG-, or RAL-based regimens	Oral bioavailability of these regimens is not significantly affected by food.
		Regimens That Should Be Taken With Food • ATV/r- or ATV/c-based regimens • DRV/r- or DRV/c-based regimens • EVG/c/TAF/FTC[a] • EVG/c/TDF/FTC[a] • RPV-based regimens	Food improves absorption of these regimens. RPV-containing regimens should be taken with ≥390 calories of food.
		Regimens That Should Be Taken on an Empty Stomach • EFV-based regimens	Food increases EFV absorption and may increase CNS side effects.
Presence of Other Conditions	Chronic kidney disease (defined as CrCl <60 mL/min)	In general, avoid TDF. ABC may be used if patient is HLA-B*5701 negative. If HIV RNA is >100,000 copies/mL, do not use ABC/3TC plus EFV or ATV/r. TAF may be used if CrCl >30 mL/min or if the patient is on chronic hemodialysis (studied only with EVG/c/TAF/FTC). Consider avoiding ATV. ART Options When ABC, TAF, or TDF Cannot Be Used (For patients with HBV coinfection, consult Hepatitis B Virus/HIV Coinfection for HBV treatment options.) • DTG/3TC (if HIV RNA <500,000 copies/mL) • DRV/r plus 3TC	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in patients using TDF in conjunction with RTV-containing regimens. An adjusted dose of TDF can be used in patients with ESRD or in those who are on hemodialysis. Refer to Appendix B, Table 11 for specific dosing recommendations. TAF has less impact on renal function and lower rates of proteinuria than TDF. ATV has been associated with chronic kidney disease in some observational studies. ABC has not been associated with renal dysfunction.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
		• DRV/r plus RAL (if CD4 count >200 cells/mm^3 and HIV RNA <100,000 copies/mL)	Avoid the use of TDF- or TAF-sparing regimens in the setting of HBV coinfection or unknown HBV status, unless also receiving a fully active HBV regimen (see Hepatitis B Virus/HIV Coinfection).
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.	Refer to Appendix B, Table 11 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	Concern for excess 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 gain than others, suggesting that particular drugs may contribute to weight gain.	Initiation of INSTI-containing regimens, particularly BIC and DTG, has been associated with greater weight gain than NNRTI-containing or boosted PI-regimens. Greater weight gain has been observed with initiation of TAF than TDF or with a switch from TDF to TAF. ARV-associated weight gain appears to disproportionately affect women and Black and Hispanic people.
	Osteoporosis	Avoid TDF.[a] ABC may be used if the patient is HLA-B*5701 negative. If HIV RNA is >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r).	TDF is associated with decreases in BMD along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF[a] and ABC are associated with smaller declines in BMD than TDF.
	Psychiatric illnesses	Consider avoiding EFV- and RPV-based regimens. Patients on INSTI-based regimens who have preexisting psychiatric conditions should be closely monitored.	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality. INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
		Some ARVs are contraindicated, and some psychiatric medications need dose adjustments when coadministered with certain ARVs.	See the drug–drug interaction tables (Tables 24a, 24b, and 24d) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.
	HIV-associated dementia	Avoid EFV-based regimens if possible.	The beneficial effects of ART on HIV-associated dementia symptoms may be confounded by EFV-related neuropsychiatric effects.
	Medication-assisted treatment for opioid use disorder	Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone. Clinical monitoring is recommended, because medications used to treat opioid dependence may need to be adjusted in some patients.	EFV reduces methadone concentrations and may lead to withdrawal symptoms. See the drug–drug interaction tables (Tables 24a, 24b, and 24d) for dosing recommendations.
	Cardiac QTc interval prolongation	Consider avoiding EFV- or RPV-based regimens if the patient is taking other medications with known risk of Torsades de Pointes or in patients at higher risk of Torsades de Pointes.	High EFV or RPV concentrations may cause QT prolongation.
	High cardiac risk	Consider avoiding ABC-based regimens. If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen. Refer to Hyperlipidemia, below, for regimens associated with more favorable lipid profiles.	An increased risk of CV events with ABC has been observed in some studies. Observational cohort studies reported an association between some PIs (DRV and LPV/r) and an increased risk of CV events; this risk has not been seen with ATV (see Protease Inhibitor-Based Regimens). Further study is needed. Certain ARV regimens are associated with more favorable lipid profiles than other regimens, although evidence on whether this improves CV outcomes is lacking.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
	Hyperlipidemia	The Following ARV Drugs Have Been Associated With Dyslipidemia: • PI/r or PI/c • EFV • EVG/c BIC, DOR, DTG, RAL, and RPV have fewer lipid effects. TDF lowers lipids; therefore, switching from TDF to TAF is associated with increased lipids.	TDF has been associated with lower lipid levels than ABC or TAF.
	Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care	Consider using regimens with a boosted PI or BIC or DTG.	These regimens have a high genetic barrier to resistance.
	Pregnancy	Refer to the Perinatal Guidelines for further guidance on ARV use during pregnancy.	
Presence of Coinfections	HBV infection	Avoid regimens that do not contain NRTIs. Use (TDF or TAF) with (FTC or 3TC) as part of the ARV regimen. If TDF and TAF Are Contraindicated • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ARV regimen (see Hepatitis B Virus/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug that is active against HBV.
	HCV treatment required	Refer to recommendations in Hepatitis C Virus/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	
	Treating TB with rifamycin antibiotics (rifabutin, rifampin, and rifapentine)	Recommended regimens may require dose adjustment. See the drug–drug interaction tables (Table 24a, Table 24b, Table 24c, Table 24d, and Table 24e) and Tuberculosis/HIV Coinfection for information on ARV use with rifamycin antibiotics.	Rifamycin antibiotics are inducers of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, and RPV.

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

[a] TAF and TDF are two FDA-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; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CAB-LA = cabotegravir long acting; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; 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; PrEP = pre-exposure prophylaxis; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; UGT = uridine diphosphate glucuronosyltransferase

Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

Updated: June 3, 2021
Reviewed: June 3, 2021

The following sections provide detailed information on antiretroviral (ARV) drugs that the Panel recommends for initial therapy for people with HIV, including the drugs' characteristics and adverse effects profiles, results from related clinical trials, and Panel recommendations on their use.

Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy–Naive Patients

Characteristics	ABC/3TC	3TC[a]	TDF/3TC	TAF/FTC	TDF/FTC
Dosing Frequency	Once daily	Once daily	Once daily	Once daily	Once daily
Available Coformulations for ART-Naive Patients	• ABC/3TC • DTG/ABC/3TC	DTG/3TC	• TDF/3TC • DOR/TDF/3TC • EFV 600 mg/ TDF/3TC • EFV 400 mg/TDF/3TC	• TAF 25 mg/FTC • BIC/TAF 25 mg/FTC • DRV/c/TAF 10 mg/FTC • EVG/c/TAF 10 mg/FTC • RPV/TAF 25 mg/FTC	• TDF/FTC • EFV/TDF/FTC • EVG/c/TDF/FTC • RPV/TDF/FTC
Adverse Effects	ABC • HSR to ABC is associated with the presence of HLA-B*5701 allele. • Increase in CV events is associated with ABC use in some cohort studies.	See below	TDF • Renal insufficiency, proximal renal tubulopathy • Decrease in BMD • Renal and bone toxicity are exacerbated by pharmacologic boosters.	TAF • Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF) • Decrease in BMD (less than with TDF; similar to with ABC) • Some studies have reported greater weight gain with TAF than with TDF.	TDF • Renal insufficiency, proximal renal tubulopathy • Decrease in BMD • Renal and bone toxicity are exacerbated by pharmacologic boosters.
	3TC: No significant adverse effects			FTC: Skin discoloration	

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy–Naive Patients

<table>
<tr><th>Characteristics</th><th>ABC/3TC</th><th>3TC[a]</th><th>TDF/3TC</th><th>TAF/FTC</th><th>TDF/FTC</th></tr>
<tr><td rowspan="2">Other Considerations</td><td colspan="3">ABC
Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to patient's allergy list.
3TC
Epivir HBV is for the treatment of HBV and contains a different dose of 3TC than the formulation for ART. Thus, Epivir HBV should not be used for HIV treatment.
Coadministration of 3TC with sorbitol-containing drugs decreases 3TC concentration and should be avoided.</td><td colspan="2">FTC should not be used as sole treatment for HBV due to development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.</td></tr>
<tr><td colspan="2">3TC or ABC/3TC should not be used as treatment for HBV due to the development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.</td><td colspan="3">Also used for HBV treatment. Discontinuation may precipitate HBV flare.
See Appendix B, Table 11 for dose recommendations in patients with renal insufficiency.</td></tr>
</table>

[a] 3TC is recommended for use with DTG in ART-naive persons and with DRV/r if ABC, TDF, and TAF are not optimal. Otherwise, dual-NRTI backbones are recommended.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; BMD = bone mineral density; CV = cardiovascular; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; NRTI = nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

The Food and Drug Administration (FDA)-approved nucleos(t)ide reverse transcriptase inhibitors (NRTIs) include zidovudine (ZDV), stavudine (d4T), didanosine (ddI), abacavir (ABC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), lamivudine (3TC), and emtricitabine (FTC). Older NRTIs (ZDV, d4T, ddI) are no longer recommended for use in clinical practice in the United States because of high rates of serious toxicities, including peripheral neuropathy and mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, lipoatrophy, and bone marrow suppression from ZDV use. The incidence of these complications is much lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.[1, 2]

ABC/3TC, TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are recommended as components of initial therapy. In addition, 3TC may be used as a single NRTI with dolutegravir (DTG), or, in select circumstances, with boosted darunavir (DRV). Table 6 provides 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. TDF is associated with lower lipid levels than TAF. Although there are insufficient data on teratogenicity in humans, TAF is now recommended as an alternative drug in pregnancy because of reassuring data from The Antiretroviral Pregnancy Registry that show no evidence of teratogenicity. Please refer to the Perinatal Guidelines. Safety, cost, and access are among the factors to consider when choosing

between these drugs. ABC/3TC, TDF/3TC, TDF/FTC, and 3TC are available as generic formulations.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in antiretroviral therapy (ART)-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug[4-6] (see the Integrase Strand Transfer Inhibitor-Based Regimen section).[7]

- 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 patients 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.[4] 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.[6]
- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative, ART-naive patients; all participants also received EFV. The primary study endpoint was renal safety of the regimens. 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%).[5]

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 noninferior to DTG plus TDF/FTC in ART-naive adults with HIV RNA <500,000 copies/mL and estimated glomerular filtration rate (eGFR) ≥50 mL/min.[8, 9]

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

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 eGFR ≥50 mL/min.

- TAF/FTC was virologically noninferior to TDF/FTC at Week 48 (92% vs. 90% of participants had plasma HIV RNA <50 copies/mL, respectively),[10] 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.[11]
- 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.[11] Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through Week 96.[12] 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.[13]

Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC, with each combination administered with boosted 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 patients demonstrated similar virologic suppression rates in both arms (75% vs. 74%).[14] In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among participants in the TAF group.
- The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At Week 48, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.[15]

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 (RTV or COBI). No significant differences appeared between unboosted TDF and TAF in terms of virologic efficacy. TAF resulted in a clinically small but statistically significant greater virologic efficacy than TDF when used with PK boosters (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 boosting. There was a small but statistically significant difference in higher rate of discontinuation due to renal adverse events in the boosted TDF subgroup compared with the boosted TAF subgroup.[16]

To assess the ability of TAF to maintain HIV and hepatitis B virus (HBV) suppression, 72 patients with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 $\log_{10}$ IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[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 $\log_{10}$ IU/mL.
- Markers of proximal tubular proteinuria and biomarkers of bone turnover decreased in those who switched to EVG/c/TAF/FTC.[17]

Although conducted in people without HIV for pre-exposure prophylaxis, 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.[18]

- TAF/FTC was noninferior to TDF/FTC for the primary endpoint of preventing HIV acquisition, and the groups did not differ statistically in overall, Grade 3–4, or serious adverse events, or in discontinuation due to adverse events.
- Changes in renal biomarkers and bone density significantly favored the TAF arm over TDF. One case of proximal tubular disease occurred in the TDF arm.
- LDL, HDL, and total cholesterol were significantly higher in the TAF arm than in the TDF arm, without significant difference in the total cholesterol to HDL ratio.

- Participants in the TAF arm gained 1.1 kg more than those in the TDF arm.

Nucleoside Reverse Transcriptase Inhibitor Options for Initial Therapy

In alphabetical order.

Abacavir/Lamivudine (ABC/3TC)

ABC plus 3TC has been studied in combination with EFV, several protease inhibitors (PIs), and DTG in ART-naive patients.[7, 19-21]

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 HLA-B*5701-positive patients who are given ABC will have a related HSR.[22, 23] HLA-B*5701 testing should be done if the use of ABC is being considered. A patient who tests positive for HLA-B*5701 should not be given ABC, and ABC hypersensitivity should be noted on the patient's allergy list. Patients 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. Patients 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.[24, 25]
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.[26-32] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[33-37]
- An analysis of data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) found that use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors.[38]
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

Other Factors and Considerations

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

- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in patients with renal dysfunction.

The Panel's Recommendations

- ABC should be prescribed only for patients who are HLA-B*5701 negative.
- On the basis of clinical trial safety and efficacy data, experience in clinical practice, and the availability of DTG/ABC/3TC as a STR, the Panel classifies DTG/ABC/3TC as a Recommended Initial Regimen for Most People with HIV (AI) (see Characteristics of Integrase Strand Transfer Inhibitors for discussion regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, atazanavir/cobicistat (ATV/c), DRV/c, darunavir/ritonavir (DRV/r), or RAL is recommended only for patients with pretreatment HIV RNA levels <100,000 copies/mL. See Table 6 for more detailed recommendations on the use of ABC/3TC with these drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

Emtricitabine (FTC) and lamivudine (3TC)

FTC and 3TC generally are used interchangeably in combination with other ARVs. In a randomized open-label comparison of FTC and 3TC in 440 patients with virologic suppression on a 3TC-containing regimen and who substituted FTC 200 mg daily for 3TC 150 mg twice daily, FTC and 3TC were equivalent for virologic suppression and similar in rates of adverse events.[39] A meta-analysis of 12 trials found no significant difference in treatment success between 3TC and FTC.[40] 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 (NVP)[41]—or with a boosted PI.[42] TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis. However, it is noteworthy that the participants in the NNRTI cohort who were taking 3TC generally had higher viral loads and lower CD4 T lymphocyte cell counts and were more likely to be using injection drugs at the start of the study than those taking FTC.[41] 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.[42] A retrospective analysis of an Italian national database found that viral resistance was more common with TDF/3TC than with TDF/FTC, but this was not observed in clinical trials.[43]

Adverse Effects

- Both FTC and 3TC have been well tolerated with no significant treatment-limiting adverse effects.
- In early clinical trials, FTC was infrequently associated with mild hyperpigmentation of palms and soles.

Other Factors and Considerations

- 3TC is now generic in the United States and can be coformulated with other drugs, as has occurred with DOR/TDF/3TC.

- Both 3TC and FTC have activity against hepatitis B but are insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of FTC or 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- The dose of FTC or 3TC should be adjusted in patients with creatinine clearance (CrCl) <50 mL/min.
- 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 **(AI).**

Lamivudine (3TC) as Single NRTI

Based on the GEMINI-1 and GEMINI-2 studies[9] that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naive patients with HIV RNA <500,000 copies/mL, 3TC may be used as a single NRTI with DTG (see Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs for more information). In addition, based on the ANDES trial, if ABC, TDF, and TAF cannot be used, 3TC can also be used as a single NRTI with DRV/r.[44] (see Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal.)

Other Factors and Considerations

- 3TC is available as an STR with DTG.
- 3TC has activity against HBV but is insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- 3TC is available in two brand-name formulations (one for HIV and the other for HBV), but the doses are different. The dose for HIV treatment is 3TC 300 mg daily.
- The dose of 3TC should be adjusted in patients with CrCl <50 mL/min.
- Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.

The Panel's Recommendations

The Panel recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People with HIV* with three exceptions. DTG/3TC **is not recommended** for—

- Individuals with HIV RNA >500,000 copies/mL,
- Individuals with HBV coinfection or whose HBV status is unknown, or
- Individuals starting ART before the results of genotypic resistance testing for reverse transcriptase are available.

Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

TAF, an oral prodrug of tenofovir (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:

- The potential for adverse kidney and bone effects is lower with TAF than with TDF. In randomized controlled trials that compared TAF and TDF in treatment-naive or virologically suppressed patients, TAF had more favorable effects on renal biomarkers and bone density than TDF.

Lipid Effects:

- In randomized controlled trials in ART-naive patients, in switch studies and in a large study of preexposure prophylaxis, levels of LDL and HDL cholesterol and triglycerides were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol to HDL ratios did not differ between patients receiving TAF and those receiving TDF. The clinical significance of this finding is not clear.[10, 45, 46]

Weight Gain:

- Initiation of TAF in ART-naive individuals and in people without HIV has been associated with greater weight gain than initiation of TDF[47, 48] and ABC.[48] Significant weight gain initially was reported in a cohort of patients switching from TDF- to TAF-containing regimens.[49] 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 patients, a greater increase in body weight was reported with initiation of TAF than with TDF.[47] Weight gain was most pronounced in Black women (10 kg over 96 weeks). This area is under intense investigation, and the clinical significance of the effect is still uncertain. It is also unclear whether change of therapy results in reversal of weight gain.

Other Factors and Considerations

- TAF/FTC is available in FDCs with bictegravir (BIC), DRV/c, EVG/c, or rilpivirine (RPV), allowing the regimens to be administered as a single pill taken once daily with food.
- In Phase 3 randomized trials, BIC/TAF/FTC was comparable to DTG/ABC/3TC and to DTG plus TAF/FTC (see Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs).
- TAF-containing regimens are approved for patients 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 patients on hemodialysis with eGFR <15 mL/min.[50]

- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ARV regimen because these drugs have activity against both viruses (see Hepatitis B Virus/HIV Coinfection).[17]
- Although there are insufficient data on teratogenicity in humans, TAF is now recommended as an alternative drug in pregnancy because of reassuring data from the Antiretroviral Pregnancy Registry that show no evidence of teratogenicity.

The Panel's Recommendation

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[51] 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, DTG, and RAL, and as part of Recommended Regimens in Certain Clinical Situations.

Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) and Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC)

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.[52-61]

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.[62, 63] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in women),[64] and preexisting renal impairment.[65] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that the risk of renal dysfunction is greater when TDF is used in these regimens. As previously noted, adverse effects on renal biomarkers, such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.[66]
- 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 boosting.[16]

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.[67, 68] BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF.

- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.[69] Adverse bone outcomes have been found to be more likely when TDF/FTC is coadministered with PK boosters. However, a recent meta-analysis found no difference in bone-related toxicities between TAF and TDF, regardless of boosting.[16]

Other Factors and Considerations

- TDF/FTC is available in FDCs with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill taken once daily.
- TDF/3TC is available in FDCs with DOR 100 mg, EFV 600 mg, and EFV 400 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). In patients who have preexisting renal insufficiency (CrCl <60 mL/min),[70] use of TDF generally should be avoided. If TDF is used, a dose adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 10 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In patients with HBV/HIV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ARV regimen because these drugs have activity against both viruses (see Hepatitis B Virus/HIV Coinfection).

The Panel's Recommendations

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most people with HIV when combined with DTG or RAL. See Table 6 for recommendations regarding use of TDF/FTC with other drugs.
- TDF should be used with caution or avoided in patients with renal disease and 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 patients taking TDF.

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Integrase Strand Transfer Inhibitor–Based Regimens

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

	BIC	DTG	EVG	RAL
Dosing Frequency	Once daily	Once Daily • In ART-naive or INSTI-naive persons Twice Daily • If used with certain CYP3A4 and UGT1A1 inducers; *or* • In INSTI-experienced persons with certain INSTI drug resistance mutations	Once daily; requires boosting with COBI	• 400 mg twice daily, *or* • 1,200 mg (two 600-mg tablets) once daily
STR Available for ART-Naive Patients	BIC/TAF/FTC	• DTG/ABC/3TC • DTG/3TC	• EVG/c/TAF/FTC • EVG/c/TDF/FTC	No
Available as an STR	No	Yes	No	Yes, but requires two tablets per dose
Virologic Efficacy Against EVG- or RAL-Resistant HIV	*In vitro* data indicate activity, but clinical trial data are not available.	Yes, for some isolates; effective with DTG 50 mg twice-daily dose	No	No
Adverse Effects	Weight gain, nausea, diarrhea, headache, insomnia; depression and suicidality are rare, occurring primarily in patients with preexisting psychiatric conditions.			
	↑ CPK 4%	Hypersensitivity, hepatotoxicity, ↑ CPK, myositis	↑ TG, ↑ LDL	↑ CPK, myopathy, hypersensitivity, SJS/TEN
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate (minor)	EVG is a CYP3A4 substrate; COBI is a CYP3A4 inhibitor	No
Chelation with Polyvalent Cation Supplements and Antacids	Oral absorption of all INSTIs may be reduced by polyvalent cations. See Table 24d for recommendations regarding dosing separation of INSTIs and these drugs.			

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

	BIC	DTG	EVG	RAL
Other Key Potential Drug Interaction Mechanisms	P-gp substrate, UGT1A1 substrate, OCT2 and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate	EVG is a UGT1A1 substrate; COBI is a P-gp inhibitor.	UGT1A1 substrate

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; COBI = cobicistat; CPK = creatine phosphokinase; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LDL = low density lipoprotein; MATE = multidrug and toxic compound extrusion; OCT2 = organic cation transporter 2; P-gp = p-glycoprotein; RAL = raltegravir; SJS/TEN = Stevens Johnson Syndrome/toxic epidermal necrolysis; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; UGT = uridine diphosphate glucuronosyltransferase+

Summary

Four integrase strand transfer inhibitors (INSTIs)—bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL)—are approved for use in antiretroviral therapy (ART)-naive patients with HIV. Cabotegravir (CAB) is a new INSTI that is approved to be used with rilpivirine (RPV) as part of a long-acting injectable complete antiretroviral (ARV) regimen to replace a stable oral regimen in patients with 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 Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends one of the following INSTI-based regimens for most people with HIV:

- BIC/tenofovir alafenamide (TAF)/emtricitabine (FTC) **(AI)**
- DTG/abacavir (ABC)/lamivudine (3TC) **(**if HLA-B*5701 negative and without chronic hepatitis B [HBV] virus coinfection) **(AI)**
- DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) with (FTC or 3TC) **(AI)**
- DTG/3TC **(AI),** except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

For a person who had exposure to CAB-LA as PrEP, an INSTI-containing regimen should not be initiated unless an INSTI genotypic resistance-test result is available and shows no INSTI-resistance mutations **(AIII).** In these cases, boosted darunavir (DRV) plus (TAF or TDF) plus (FTC or 3TC) should be used, pending INSTI resistance results if treatment is initiated before genotypic test results are available **(AIII).**

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

EVG and RAL have a lower barrier to resistance than BIC and DTG. Because of their high barrier to resistance, DTG plus two nucleoside reverse transcriptase inhibitors (NRTIs) or BIC/TAF/FTC may

be considered for patients who must start ART before resistance test results are available. RAL is not available in a single-tablet regimen (STR) formulation, and RAL-containing regimens have a higher pill burden than BIC- and DTG-containing regimens. EVG-based regimens require pharmacokinetic (PK) boosting with cobicistat (COBI), which results in a greater potential for interaction with concomitant medications. Both EVG- and RAL-based regimens are considered *Recommended Initial Regimens in Certain Clinical Situations*.

All INSTIs are generally well tolerated, although there are reports of insomnia in some patients. Depression and suicidal ideation, primarily in patients with a history of psychiatric illnesses, have been reported rarely in patients receiving INSTI-based regimens.[1-4]

Among ARV-naive individuals, initiation of INSTI-containing regimens has been associated with greater weight gain than non-nucleoside reverse transcriptase inhibitor (NNRTI)- or boosted protease inhibitor (PI)-regimens.[5-10] 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 elvitegravir/cobicistat (EVG/c) or with efavirenz (EFV).[7,11-13] Greater weight gain also has been observed after initiation of TAF[6,7,14] or with a switch from TDF to TAF,[15] especially in conjunction with INSTIs. Although ARV-associated weight gain appears to disproportionately affect women and Black and Hispanic people,[5-7,16] predictors and mechanisms for the weight gain are still unclear. Further questions that need to be clarified include regional distribution of the weight gain,[17] whether it is associated with significant cardio-metabolic risk,[18] and whether it is reversible upon discontinuation of the offending agent.

INSTIs in Persons of Childbearing Potential

- Earlier data from a birth outcomes surveillance study in Botswana raised concern of an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[19,20] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[21] Based on these data, the Panel considers DTG an option for persons of childbearing potential. Clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision. See the Dolutegravir section in the Perinatal Guidelines for more detail.
- BIC **is not currently recommended** during pregnancy due to insufficient data on safety and efficacy.
- EVG/c should not be initiated in people who are pregnant or planning to become pregnant because of inadequate drug concentrations in the second and third trimesters. Refer to the Perinatal Guidelines for further guidance.
- Data on RAL use around the time of conception are limited. Based on data collected from the Antiretroviral Pregnancy Registry, the drug manufacturer, and a cohort study from the United States and other countries, no cases of NTDs have been reported.[22-24] Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.[22-24] RAL remains an option for an INSTI-based regimen in persons of childbearing potential.

Clinicians should refer to the Perinatal Guidelines for detailed recommendations on ARV regimens in treatment-naive patients, including on the use of INSTI-based regimens during conception and throughout pregnancy.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen for Most People with HIV

Bictegravir (BIC)

BIC is an INSTI that is approved by the U.S. Food and Drug Administration for initial therapy in adults with HIV as a component of an STR, once-daily regimen with TAF and FTC.

Efficacy in Clinical Trials

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3, randomized double-blind, clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at Week 48.
    - The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At Week 96, 84% of participants in the BIC arm and 86% of those in the DTG arm achieved HIV RNA <50 copies/mL.[14]
    - 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.[25]
    - Week 144 follow-up from both trials demonstrated noninferiority of the BIC/TAF/FTC regimen to both DTG-containing regimens, with high levels of virologic suppression and no treatment-emergent resistance. Weight gain was seen across all treatment groups in both studies, with no differences in median changes from baseline in weight at Week 144 for either study. Median weight gain was 4.1 kg in the BIC/TAF/FTC group and 3.5 kg in the DTG/ABC/3TC group in GS-US-1489. In GS-US-1490, median weight gain was 4.4 kg in the BIC/TAF/FTC group and 5.0 kg in the DTG/TAF/FTC group.[11]

Adverse Effects

- BIC is generally well tolerated. In clinical trials, the most commonly reported adverse reactions of any grade with an incidence ≥5% included diarrhea, nausea, and headache.
- As discussed in the Summary section above, some studies have shown greater weight gain among people initiating INSTI-based regimens, particularly Black women. 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).[7]
- Serious neuropsychiatric adverse events were uncommon (<1%) in clinical trials, and mainly occurred in the setting of preexisting depression or other psychiatric illness or prior suicide attempt.[26]

Other Factors and Considerations

- BIC is a cytochrome P450 (CYP) 3A4 substrate and a uridine diphosphate glucuronosyltransferase (UGT) 1A1 substrate, and its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in a loss of therapeutic effect. For patients who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anticonvulsants and St. John's wort also should be avoided.[26]
- BIC is an inhibitor of the drug transporters OCT2 and MATE1, which may lead to increased concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.
- BIC is not a CYP3A4 inducer or inhibitor; thus, unlike EVG/c, BIC is unlikely to affect the metabolism of medications that are CYP3A4 substrates.
- 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, or calcium or iron supplements). See Drug–Drug Interaction Table 24d for details on dosing BIC with polyvalent cations.
- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are observed typically within the first 4 weeks of BIC therapy (with a median increase of 0.10 mg/dL after 48 weeks). This increase is comparable to that seen with other drugs that have a similar effect on creatinine secretion, including DTG, RPV, and COBI.
- Treatment-emergent mutations that confer BIC resistance have not yet been reported in people receiving BIC for initial therapy. BIC has not been studied in people with prior INSTI failure or INSTI-related resistance mutations and, therefore, should not be used in these individuals until more data are available.
- Data are insufficient to determine whether use of BIC around the time of conception and during pregnancy is safe.

The Panel's Recommendation

- Based on clinical trial data, the Panel categorizes the combination of BIC/TAF/FTC administered once daily as a *Recommended Initial Regimen for Most People with HIV* **(AI).**
- BIC should not be used during pregnancy because of insufficient safety data.

Dolutegravir (DTG)

DTG is an INSTI with a higher barrier to resistance than EVG or RAL. In ART-naive patients, DTG plus two NRTIs demonstrated high efficacy in achieving HIV suppression. DTG is given once daily, with or without food.

Efficacy in Clinical Trials

- The efficacy of DTG in ART-naive patients has been evaluated in several fully powered randomized controlled clinical trials. In these trials, DTG-based regimens were noninferior or superior to a comparator INSTI-, NNRTI-, or PI-based regimen. The primary efficacy endpoint

in these clinical trials was the proportion of participants with plasma HIV RNA <50 copies/mL.[12,27,28]

DTG plus Two NRTIs versus Other INSTIs plus Two NRTIs:

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared to BIC/TAF/FTC in two randomized controlled trials. These regimens have shown virologic efficacy that is similar to BIC/TAF/FTC (see discussion in the BIC section above).[14,25,27,29]
- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily. Each drug was administered in combination with an investigator-selected, two-NRTI combination (ABC/3TC or TDF/FTC) to 822 participants. At Week 96, DTG was noninferior to RAL.[30]

DTG plus Two NRTIs versus EFV plus Two NRTIs:

- The SINGLE trial compared DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At Week 48, DTG plus ABC/3TC was superior to EFV/TDF/FTC, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.[31] At Week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[32]
- The ADVANCE trial, an open-label, noninferiority trial conducted in South Africa, compared DTG with either TDF/FTC or TAF/FTC to EFV/TDF/FTC. At Week 96, the DTG-based regimens were noninferior to the EFV regimen based on the proportion of participants with HIV RNA levels <50 copies/mL (79% in DTG/TAF/FTC vs. 78% in DTG/TDF/FTC vs. 74% in EFV/TDF/FTC arms). More participants discontinued the trial regimen in the EFV group than in the DTG group. Mean weight gain was 7.1 kg in the DTG/TAF/FTC group, 4.3 kg in the DTG/TDF/FTC group, and 2.3 kg in the EFV/TDF/FTC) and was greater among women than men.[13]
- The NAMSAL ANRS 12313 study, an open-label, multicenter randomized noninferiority trial conducted in Cameroon, compared DTG to EFV 400 mg, both combined with TDF/3TC. At Week 96, DTG was noninferior to EFV 400 mg, with HIV RNA <50 copies/mL in 74% and 72% of participants in the DTG and EFV arms, respectively. Virologic suppression was reached more rapidly in the DTG group, and no DTG resistance mutations were acquired through Week 96. Median weight gain was 5.0 kg in the DTG group versus 3.0 kg in the EFV group.[12,33]

DTG plus Two NRTIs versus Ritonavir-boosted Protease Inhibitor (PI/r) plus Two NRTIs:

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to 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. The rate of participants who discontinued their assigned regimen was higher in the DRV/r arm.[34] The difference in efficacy between the DTG and DRV/r regimens was more pronounced in patients with pre-treatment HIV RNA levels >100,000 copies/mL. At Week 96, DTG remained superior to DRV/r.[35]
- The ARIA trial, an open-label, Phase 3b randomized controlled trial, compared the efficacy and safety of DTG/ABC/3TC to atazanavir/ritonavir (ATV/r) plus TDF/FTC in ART-naive, nonpregnant women. At Week 48, 82% of participants in the DTG group and 71% in the ATV/r

group (P = 0.005) achieved HIV RNA <50 copies/mL. The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.[28]

DTG/3TC:

- In the GEMINI-1 and GEMINI-2 trials, 1,433 ART-naive participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive DTG plus 3TC or DTG plus TDF/FTC. At Week 96, DTG plus 3TC was noninferior to DTG plus TDF/FTC 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).[36] 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 INSTI resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the rate of those 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 failure in the two-drug group. Overall mean change in weight from baseline was 3.1 kg in the DTG plus 3TC group and 2.1 kg in the DTG plus TDF/FTC group. At Week 144, DTG plus 3TC maintained noninferiority to DTG plus TDF/FTC with 82% versus 84% of participants maintaining viral load <50 copies/mL, respectively. The proportion of participants with viral load ≥50 copies/mL was 3% in both treatment groups. A lower risk of drug-related adverse events was found with DTG plus 3TC versus DTG plus TDF/FTC (20% vs. 27%; relative risk, 0.76 [95% CI, 0.63–0.92]).[36]
- Two other small, nonrandomized single-arm studies showed similar rates of viral suppression with DTG plus 3TC.[37,38]

Adverse Effects

- DTG is generally well tolerated. The most reported adverse reactions of moderate-to-severe intensity were insomnia and headache.
- As discussed in the Summary section above, some studies have shown greater weight gain among people initiating INSTI-based regimens, including regimens with DTG.[6,7,39,40] 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).[7]
- Neuropsychiatric adverse events (e.g., sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and other INSTIs have been reported.[1,2] 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.[41] Neuropsychiatric events rarely led to DTG discontinuation. Data on BIC are more limited because of its recent licensure.

Other Factors and Consideration

- DTG, like BIC, decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment.
- DTG has fewer drug interactions than EVG/c. See Table 24d for specific drug–drug interactions that require dosage adjustment.

- DTG absorption, like absorption for other INSTIs, may be reduced when the ARV is coadministered with polyvalent cations (see Table 24d). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives are taken. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have been rarely reported in patients receiving DTG as part of a three-drug regimen for initial therapy.[42-44] 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

- Based on clinical trial data, the Panel categorizes DTG in combination with ABC/3TC **(AI),** TAF/FTC **(AI),** or TDF/(FTC or 3TC) **(AI)** as a *Recommended Initial Regimen for Most People with HIV*.
- The Panel also recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People with HIV*, except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or of HBV testing are available.
- Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen in Certain Clinical Situations

Elvitegravir (EVG)

EVG is available as a component of two STRs: EVG/c/TDF/FTC and EVG/c/TAF/FTC. COBI is a specific, potent CYP3A inhibitor that has no activity against HIV. It acts as a PK enhancer of EVG, which allows once-daily dosing of the combination but increases the likelihood of significant drug interactions.

Efficacy in Clinical Trials

- The efficacy of EVG/c/TDF/FTC in ART-naive participants has been evaluated in two randomized, double-blind, active-controlled trials.
  - At 144 weeks, EVG/c/TDF/FTC was noninferior to fixed-dose EFV/TDF/FTC.[45]
  - EVG/c/TDF/FTC also was found to be noninferior to ATV/r plus TDF/FTC.[46]
  - In a randomized blinded trial that compared EVG/c/TDF/FTC to ATV/r plus TDF/FTC in women with HIV, EVG/c/TDF/FTC had superior efficacy, in part, due to a lower rate of treatment discontinuation.[47]
- The efficacy of EVG/c/TAF/FTC in ART-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min.[48,49]
  - At 48 and 96 weeks, TAF was noninferior to TDF when both drugs were combined with EVG/c/FTC; at 144 weeks, EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC.[50]

Adverse Effects

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[45,46]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[26]
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see discussion in the DTG section above).

Other Factors and Considerations

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI is a PK enhancer, it is a CYP3A enzyme inhibitor, which may lead to significant interactions with medications that are metabolized by this enzyme (see Table 24d).[51]
- Administration of EVG simultaneously with polyvalent cation-containing antacids or supplements lowers EVG plasma concentrations (see Table 24d). Separate administration of EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacids by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG.
- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated creatinine clearance (CrCl) without reducing glomerular function.[52] Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be monitored closely and evaluated for evidence of TDF-related proximal renal tubulopathy.[26]
- EVG/c/TDF/FTC **is not recommended** for patients with pre-treatment estimated CrCl <70 mL/min.[26]
- EVG/c/TAF/FTC **is not recommended** for patients with estimated CrCl <30 mL/min unless they are on chronic hemodialysis. An observational study of 55 people with HIV who were on hemodialysis suggested that EVG/c/TAF/FTC given once daily (after hemodialysis on dialysis days) can be used safely in persons with no resistance to any of the ARV drugs in this STR.[53]
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.[45,46] These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.
- EVG/c **is not recommended** during pregnancy due to low drug exposure when taken during the second and third trimesters.[54]

The Panel's Recommendation

- Based on the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as *Recommended Initial Regimens in Certain Clinical Situations* **(BI).** EVG/c/TAF/FTC should be used only in people with estimated CrCl ≥30 mL/min unless they are on chronic hemodialysis. EVG/c/TDF/FTC should be used only in people with estimated CrCl ≥70 mL/min.

Raltegravir (RAL)

RAL was the first INSTI approved for use in both ARV-naive and ARV-experienced patients.

Efficacy in Clinical Trials

RAL 400 mg Twice Daily plus Two NRTIs versus Comparator Drug plus Two NRTIs:

- The efficacy of RAL at a dose of 400 mg twice daily (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials and a third open-label randomized trial.
    - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each administered in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.[55] RAL was superior to EFV at 4 and 5 years,[56,57] in part, because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
    - The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At Week 96, DTG was noninferior to RAL. At 48 weeks, no treatment-emergent resistance had occurred in those with virologic failure in the DTG arm, but in the RAL arm, one patient had an INSTI-resistance mutation and four had NRTI-resistance mutations.[58]
    - The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 participants with baseline viral loads ≥100,000 copies/mL and 125 participants with baseline viral loads <100,000 copies/mL) received RAL in combination with ABC/3TC. After 96 weeks, no difference in virologic response was evident between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.[30]
    - ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens that contained RAL, ATV/r, or DRV/r, each given with TDF/FTC. At Week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the PI/r arms than in the RAL arm, and bone mineral density decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.[59]

RAL 1,200 mg Once Daily plus TDF/FTC versus RAL 400 mg Twice Daily plus TDF/FTC:

- In a Phase 3 randomized, double-blind, active comparator-controlled trial (the ONCEMRK trial), the efficacy of once-daily RAL 1,200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each administered with TDF/FTC. At 96 weeks, a similar proportion of participants in both groups achieved HIV RNA suppression (81.5% in the once-daily arm vs. 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 count.[60]

Adverse Effects

- RAL, when compared in a randomized trial to DRV/r or ATV/r, all with TDF/FTC, led to a greater mean increase in waist circumference.[61]

- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic hypersensitivity reactions in patients who received RAL have been reported during post-marketing surveillance.[62]
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, suicidal ideation) have been reported in people receiving INSTIs (see discussion in the DTG section above).[41,63]

Other Factors and Considerations

- RAL can be administered as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily with or without food in ART-naive patients. RAL is not available as an STR.
- Coadministration of RAL as either 400 mg twice daily or 1,200 mg once daily with aluminum-containing and/or magnesium-containing antacids **is not recommended.** Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1,200 mg once daily. Polyvalent cation-containing supplements also may reduce absorption of RAL. See Table 24d for dosing recommendations.
- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.
- Data on RAL use around the time of conception are limited. Thus far, based on data collected from the Antiretroviral Pregnancy Registry, the drug manufacturer, and a cohort study from the United States and other countries, no cases of NTDs have been reported.[22-24] Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.[22-24] RAL remains an option for an INSTI-based regimen for persons of childbearing potential.

The Panel's Recommendations

- Based on these clinical trial data, the Panel considers RAL given as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily plus TDF/FTC **(BI)** or TAF/FTC **(BII)** as a *Recommended Initial Regimen in Certain Clinical Situations*.

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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Non-Nucleoside Reverse Transcriptase Inhibitor–Based Regimens

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Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)That Are Recommended as Initial Therapy for People with HIV

Characteristics	DOR	EFV	RPV[a]
Dosing Frequency	Once daily	Once daily	Once daily
Food Requirement	With or without food	On an empty stomach	With a meal
STR Available for ART-Naive Patients	DOR/TDF/3TC	• EFV 600 mg/TDF/FTC • EFV 600 mg/TDF/3TC • EFV 400 mg/TDF/3TC	• RPV/TAF/FTC • RPV/TDF/FTC
Available as a Single-Drug Tablet	Yes	Yes	Yes
Adverse Effects	Generally well tolerated	• CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, insomnia, somnolence • Skin rash • QTc prolongation	• Depression, headache • Skin rash • QTc prolongation
CYP3A4 Drug–Drug Interactions	CYP3A4 substrate	CYP3A4 substrate, mixed inducer/inhibitor	CYP3A4 substrate
Other Significant Drug Interactions	None	CYP2B6 and 2C19 inducer	RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is not recommended; see Drug–Drug Interactions for dosing recommendations when RPV is coadministered with H2 blocker or antacids.

[a] See Optimizing Antiretroviral Therapy section and Appendix B, Table 4 for information regarding injectable RPV.

Key: 3TC = lamivudine; ART = antiretroviral therapy; CNS = central nervous system; CYP = cytochrome P; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

Five NNRTIs—delavirdine (DLV), doravirine (DOR), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), and rilpivirine (RPV) are currently approved by the Food and Drug Administration (FDA) for the treatment of HIV when used in combination with other antiretroviral (ARV) drugs. This section of the guidelines will focus on DOR, EFV, and RPV, the three NNRTIs recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) as part of an initial antiretroviral therapy (ART) regimen for people with HIV in certain clinical scenarios (see Table 6 and Table 7).

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs (especially EFV and RPV) are the prevalence of NNRTI-resistant viral strains in ART-naive patients[1] and the drugs' low barrier for the development of resistance. Resistance testing should be performed before initiation of an NNRTI-based regimen in ART-naive patients. High-level resistance to all NNRTIs (except ETR or DOR) may occur with a single mutation. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.[2,3] DOR-, EFV-, and RPV-based regimens are now categorized as *Recommended Initial Regimens in Certain Clinical Situations* for ART-naive patients. More details about these NNRTI are provided below.

Doravirine (DOR)

Efficacy in Clinical Trials

The efficacy of DOR-based therapy for treatment of HIV in ART-naive individuals was demonstrated in two randomized, double-blind, placebo-controlled trials.

DOR-Based Regimen versus EFV-Based Regimen

- In the DRIVE-AHEAD trial 734 participants received either DOR/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or EFV/TDF/emtricitabine (FTC), both as a daily fixed-dose tablet.[4]
  - At 96 weeks, DOR/TDF/3TC was noninferior to EFV/TDF/FTC, with 77.5% of participants who received DOR/TDF/3TC and 73.6% of those who received EFV/TDF/FTC achieving HIV RNA <50 copies/mL. Although virologic responses to ART overall were lower in participants with pre-treatment HIV RNA >100,000 copies/mL or pre-treatment CD4 counts of ≤200 cells/mm^3, there was no difference between the DOR-treated and EFV-treated participants.
  - Virologic rebound and virologic nonresponse were similar in the DOR/TDF/3TC (9.3%) and EFV/TDF/FTC (7.7%) treatment groups. At 96 weeks, genotype resistance results were reported for 21 participants with protocol defined virologic failure in the DOR arm and 15 participants in the EFV arm. For the DOR arm, 7 out of 21 participants had NNRTI resistance and 6 out of 21 had NRTI resistance. For EFV, 10 of 15 participants had NNRTI resistance and 5 of 15 had NRTI resistance.
  - More participants in the EFV arm discontinued their assigned ART due to adverse events than in the DOR arm (6.6% vs. 3.0%). Neuropsychiatric side effects and rash were more common in the EFV arm.
  - Low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol did not change with DOR use, whereas both increased with EFV use.

DOR-Based Regimen versus Darunavir/Ritonavir (DRV/r)-Based Regimen

- In the DRIVE-FORWARD trial, 769 participants received DOR or DRV/r once daily along with two investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs), either abacavir (ABC)/3TC or TDF/FTC.[5]
  - At 48 weeks, DOR was found to be noninferior to DRV/r with 84% of study participants receiving DOR versus 80% of those receiving DRV/r achieving HIV RNA <50 copies/mL at

48 weeks. Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.

- At Week 96, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).[6] Treatment responses were similar regardless of baseline characteristics.
- Virologic failure by Week 96 was low and similar in the DOR and DRV/r groups (9% vs. 11%). Genotype resistance results were reported for 11 and 14 participants with virologic failure in the DOR and DRV/r arms, respectively. Treatment-emergent resistance to any study drug occurred in 2 (1%) of 383 participants in the DOR group and 1 (<1%) of 383 participants in the DRV/r group.
- Treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases in fasting LDL cholesterol, triglycerides, non-HDL cholesterol, and total cholesterol were seen in the participants who received DRV/r than in those who received DOR.

Other Factors and Considerations

- DOR is available as a single-drug, 100-mg tablet[7] and as part of an single-tablet regimen (STR) that contains DOR/TDF/3TC 100 mg/300 mg/300 mg[8] and is dosed once daily, with or without food.
- DOR-based regimens have not been directly compared to integrase strand transfer inhibitor (INSTI)-based regimens in clinical trials, and has not been studied with tenofovir alafenamide (TAF) in clinical trials.
- A post hoc analysis of three randomized controlled trials examined weight gain among ART-naive participants receiving DOR versus DRV/r or EFV. At week 96, mean weight gain was similar in the DOR group (2.4 kg), the DRV/r group (1.8 kg), and the EFV group (1.6 kg). No significant differences between treatment groups were found in the proportion of participants whose BMI class increased to overweight or obese at Week 48 or Week 96.[9]
- DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see Table 24b). DOR is not a CYP3A4 inducer or inhibitor, so it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.[10]
- There are currently no data on the safety of DOR use during pregnancy.
- There are limited clinical trial data with the combination of DOR + ABC/3TC so the Panel is less certain about the efficacy of this regimen.

The Panel's Recommendations

- On the basis of 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 *Recommended Initial Regimens in Certain Clinical Situations*.

Efavirenz (EFV)

Efficacy of EFV 600-mg Daily Dose in Clinical Trials

- Large randomized controlled trials and cohort studies in ART-naive patients have demonstrated potent and durable viral suppression in patients treated with EFV plus two NRTIs. EFV-based regimens have demonstrated superiority or noninferiority to a number of comparator regimens in ART-naive patients in several randomized controlled trials.
- In the AIDS Clinical Trials Group (ACTG) 5202 study, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[11]
- In the Evidence for Contraceptive Options in HIV (ECHO) and Targeting HIV Retention and Improved Viral Load Through Engagement (THRIVE) studies, EFV was noninferior to RPV, with less virologic failure. However, EFV caused more discontinuations due to adverse events. The virologic advantage of EFV was most notable in participants with pre-ART viral loads >100,000 copies/mL, and NRTI and NNRTI resistance occurred more frequently in patients who experienced failure on a regimen that included RPV.[12]
- In the Gilead Sciences (GS) 102 study, EFV/TDF/FTC was noninferior to elvitegravir/cobicistat [EVG/c]/TDF/FTC.[13]
- The DRIVE-AHEAD study compared EFV/TDF/FTC to DOR/TDF/3TC in ART-naive patients. At 96 weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, as discussed in the DOR section. Neuropsychiatric side effects were more common in the EFV arm.[4]
- ADVANCE, an open-label, noninferiority trial conducted in South Africa, compared TDF/FTC/EFV 600 mg with dolutegravir (DTG) combined with either TDF/FTC or TAF/FTC. At Week 96, the DTG regimens were noninferior to the EFV regimen based on the proportion of participants with HIV-RNA levels <50 copies/mL (79% in DTG/TAF/FTC vs. 78% in DTG/TDF/FTC vs. 74% in EFV/TDF/FTC arms). More participants in the EFV group discontinued the trial regimen 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), and was greater among women than men [14]

In clinical trials, some regimens have demonstrated superiority to those with EFV, based primarily on fewer discontinuations because of adverse events:

- In the SINGLE trial, a DTG-based regimen was superior to an EFV regimen at the primary endpoint of viral suppression at Week 48.[15]
- In the STARTMRK trial, raltegravir (RAL) was noninferior to EFV at 48 weeks,[16] but RAL was superior to EFV at 4 and 5 years,[17,18] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
- In the open-label Single-Tablet Regimen (STaR) trial, participants with baseline viral loads ≤100,000 copies/mL had higher rates of treatment success on RPV than on EFV.[19]

Efficacy of Low-Dose Efavirenz (EFV 400 mg Daily) in Clinical Trials

- ENCORE 1, a multinational, randomized, placebo-controlled trial, compared two once-daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg

(reduced dose). At 96 weeks, EFV 400 mg was noninferior to EFV 600 mg for rate of viral suppression.[20] While the frequency of overall adverse events was not different between groups, EFV-related adverse events and treatment-related discontinuations occurred less frequently in the EFV 400 mg group than in the EFV 600 mg group. Although there were fewer self-reported central nervous system (CNS) events in the 400 mg group, the groups had similar rates of psychiatric events. The 400-mg dose of EFV is now approved in the United States for initial treatment of HIV infection and is coformulated with TDF and 3TC in a fixed-dose combination (FDC) tablet.

- NAMSAL ANRS 12313, an open-label, multicenter randomized noninferiority trial conducted in Cameroon, compared EFV 400 mg with DTG, both combined with TDF/3TC. At Week 96, EFV 400 mg was noninferior to DTG based on percentage of participants with viral suppression to HIV RNA <50 copies/mL (72% in EFV group vs. 74% in DTG group). Virologic suppression was reached more rapidly in the DTG group. Among nine virologic failures in the DTG arm, there were no acquired DTG resistance mutations through Week 96. A total of 19 virologic failures occurred in the EFV arm, with 17 having resistance mutations to EFV. Median weight gain was 5.0 kg in the DTG group versus 3.0 kg in the EFV group.[21,22]
- In an open label trial, 25 pregnant women with HIV and HIV RNA <50 copies/mL while on an EFV-based regimen were switched from EFV 600 mg to EFV 400 mg daily (the TDF and FTC or 3TC components of the regimen did not change). Participants were monitored closely with EFV concentrations measured weekly and viral loads biweekly during pregnancy and postpartum. Stopping criteria were HIV RNA >50 copies/mL on two consecutive occasions or random EFV concentration <800 ng/mL on three consecutive occasions. All participants maintained viral load suppression to HIV RNA <50 copies/mL throughout the study.[23]
- A pharmacokinetic (PK) study enrolled 22 people with HIV (without tuberculosis) who were on an EFV-based regimen and had HIV RNA levels <50 copies/mL. Participants were switched from EFV 600 mg to EFV 400 mg. Fourteen days after the switch, isoniazid and rifampin were started for 12 weeks. The combination resulted in only minimal reduction in EFV 400 mg PK parameters, which were within the range of concentrations seen in the ENCORE 1 trial. HIV RNA levels <50 copies/mL were maintained in all participants during the study.[24]

Adverse Effects

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, depression) that resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur.
- EFV use has also been associated with suicidality; however, evidence for this association has differed among various large studies. An analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e., reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (lopinavir/ritonavir [LPV/r], atazanavir (ATV), atazanavir/cobicistat (ATV/r), or ABC-based regimens).[25] Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behavior among participants in the immediate ART group who took EFV than among ART-naive controls; the risk increased for those with previous psychiatric diagnoses.[26] This association, however, was not found in analyses of three large observational cohorts[27,28] or in a retrospective cohort study that used U.S. administrative pharmacy claims data.[29] A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried a greater risk of suicidal ideation or depression than NVP.[30]

- Delayed onset neurotoxicities, including ataxia and encephalopathy, have been reported months to years after EFV use.[31,32]
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.[33,34] Consider an alternative to EFV in patients taking medications known to increase the risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.

Other Factors and Considerations

- EFV is formulated both as a single-drug, 600-mg tablet and in an FDC tablet of EFV/TDF/FTC that allows for once-daily dosing.
- EFV is also available as a generic single-drug, 600-mg tablet and as a generic once-daily FDC tablet that includes 3TC, TDF, and either 600 mg or 400 mg of EFV; the lower-dose EFV/TDF/3TC tablet is approved for treating adults and children weighing ≥35 kg.[35,36]
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6, and therefore, may potentially interact with other drugs that use the same pathways (see Tables 24b, 25a, and 25b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.[37] A link between EFV and birth defects in humans has not been supported in meta-analyses or data on more than 7,900 periconception exposures from Botswana (see the Perinatal Guidelines).[38,39]
- People with HIV who are taking a regimen that includes EFV should be screened for depression and suicidality.

The Panel's Recommendations

- Given the availability of regimens with fewer treatment-limiting adverse events and noninferior or superior efficacy, the Panel classifies EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC **(BI)** or EFV 600 mg plus TAF/FTC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- Randomized clinical trial data have demonstrated the noninferiority of EFV 400 mg compared with EFV 600 mg[20] and to DTG.[21,22] This dose has not been studied in a U.S. population. The Panel classifies EFV 400 mg/TDF/3TC as a *Recommended Initial Regimen in Certain Clinical Situations* **(BI)**.

Rilpivirine (RPV)

RPV is an NNRTI where the oral formulation is approved for use in combination with two NRTIs for ART-naive patients with pretreatment viral loads <100,000 copies/mL. RPV is also approved as an extended-release injectable suspension as part of a long acting injectable complete ARV regimen when used with cabotegravir (CAB), an INSTI. This regimen is approved to replace oral ART in patients with virologic suppression and no history of resistance to RPV or INSTIs (see the Optimizing Antiretroviral Therapy in the Setting of Viral Suppression section for discussion of long-acting CAB/RPV).

Efficacy in Clinical Trials

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.[12] At 96 weeks, the following findings were reported:
  - RPV was noninferior to EFV overall.
  - Among participants with pre-ART viral loads >100,000 copies/mL, more RPV-treated participants than EFV-treated participants experienced virologic failure. NNRTI and NRTI resistance were more frequently identified in participants with virologic failure in the RPV group.
  - Among the RPV-treated participants, the rate of virologic failure was greater in those with pretreatment CD4 counts <200 cells/mm^3 than in those with CD4 counts ≥200 cells/mm^3.
- STaR, a Phase 3b, open-label study, compared the FDCs of RPV/TDF/FTC and of EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks[40] were similar to those reported at 48 weeks.[19]
  - RPV was noninferior to EFV overall.
  - RPV was superior to EFV in patients with pre-ART viral loads ≤100,000 copies/mL and noninferior in those with pre-ART viral loads >100,000 copies/mL. Among patients with pre-ART viral loads >500,000 copies/mL, virologic failure was more common in RPV-treated patients than in EFV-treated patients.
  - There were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (4% vs. 1%, respectively).
- The STR of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence study. In this study, plasma concentrations of RPV, FTC, and TAF 25 mg in participants taking the coformulated drug were similar to those seen in participants who received RPV as the single-drug tablet and TAF/FTC as part of the STR of EVG/c/TAF 10 mg/FTC.[41]

Adverse Effects

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of CNS adverse events (e.g., abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than in the EFV arms, and fewer patients 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. Patients receiving RPV who have severe depressive symptoms should be evaluated to assess whether the symptoms may be due to RPV and if the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations

- Oral RPV is formulated both as a single-drug tablet and in STRs with TAF/FTC with TDF/FTC and with DTG. Among available STRs, RPV/TAF/FTC is the smallest tablet.
- RPV is also available as part of a long-acting injectable ARV regimen for use in combination with long-acting CAB in patients who are virologically suppressed and do not have resistance to these drugs (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).

- RPV/TAF/FTC and RPV/TDF/FTC are given once daily and must be administered with a meal (containing at least 390 kcal).
- RPV is also coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for people with HIV who have achieved viral suppression.[42] However, this combination has not been studied in ART-naive individuals, and it **is not recommended** for initial therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- The oral drug absorption of RPV can be significantly reduced in the presence of acid-lowering agents. RPV is **contraindicated** in patients who are receiving proton pump inhibitors (PPIs), and should be used with caution in those receiving H2 antagonists or antacids (see Drug–Drug Interactions for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug–Drug Interactions).
- At doses above the approved dose of 25 mg, RPV may cause QTc interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

The Panel's Recommendations

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, the Panel recommends RPV/TDF/FTC and RPV/TAF/FTC as *Recommended Initial Regimens in Certain Clinical Situations*.
- Use of RPV with TAF/FTC **(BII)** or TDF/FTC **(BI)** should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 counts >200 cells/mm^3.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

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Protease Inhibitor–Based Regimens

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Table 8d. Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV

Characteristic	ATV	DRV
Dosing Frequency	Once daily	• Once daily for PI-naive patients • Twice daily for PI-experienced patients with certain PI mutations
PK Boosting	PK boosting with RTV or COBI generally is recommended. Unboosted ATV also is FDA-approved for ART-naive patients.	DRV only should be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	ATV/c	• DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	• Jaundice • Indirect hyperbilirubinemia • Cholelithiasis • Nephrolithiasis • PR prolongation	• Skin rash • Increase in serum transaminases • Hyperlipidemia • A higher cardiovascular risk was reported in participants taking DRV-based regimens than in those taking ATV-based regimens in an observational cohort study.
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate, inhibitor	CYP34A substrate, inhibitor
Other Significant Drug Interactions	ATV absorption is reduced when ATV is given with acid-lowering therapies. See Table 24a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents.	N/A

Key: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; N/A = not applicable; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

The U.S. Food and Drug Administration (FDA)-approved protease inhibitors (PIs) include atazanavir (ATV), ATV/cobicistat (ATV/c), darunavir (DRV), darunavir/cobicistat (DRV/c), fosamprenavir (FPV), indinavir (IDV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and tipranavir (TPV). PI-based regimens using pharmacokinetic (PK) enhancement with

either cobicistat (COBI) or RTV (also called PK boosting) increase concentration and prolong the half-lives of the PI. These regimens have demonstrated virologic potency, durability in treatment-naive patients, and a high barrier to resistance. Because LPV/r, FPV/r, unboosted ATV, and SQV/r have disadvantages, such as greater pill burden, lower efficacy, or increased toxicity, only boosted DRV and ATV in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) are recommended as initial therapy in certain clinical situations.

Because transmitted PI resistance is uncommon, boosted ATV or DRV-based regimens are recommended for rapid antiretroviral therapy (ART) initiation or in the setting of acute HIV infection, before resistance test results are available. As few or no PI mutations are detected when a patient's first PI-based regimen fails, which is not the case with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and some integrase strand transfer inhibitor (INSTI)-based regimens,[1] PI-based regimens may be useful for patients at risk for intermittent therapy because of poor adherence.

All recommended PIs require PK boosting with either RTV or COBI to inhibit the CYP3A4 isoenzyme, which may lead to significant drug-drug interactions (see Drug–Drug Interactions). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of the two recommended PIs are listed in Appendix B, Table 9 and Appendix B, Table 5. Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[2-5] Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens than in those receiving other regimens.[6]

Darunavir/Ritonavir (DRV/r)

Efficacy in Clinical Trials

- The ARTEMIS study compared DRV/r (800 mg/100 mg once daily) with LPV/r (800 mg/200 mg once daily or 400 mg/100 mg twice daily), both administered in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at Week 48[7] and superior at Week 192.[8]
- The FLAMINGO study compared DRV/r with dolutegravir (DTG), each administered in combination with two NRTIs, in 488 participants who were ART-naive. The rate of virologic suppression at Week 96 was significantly greater among those who received DTG than in those who received DRV/r. The higher rate of virologic failure observed in the DRV/r group was related primarily to the number of failures among those with a viral load >100,000 copies/mL and secondarily to more drug discontinuations in the DRV/r group.[9]
- ACTG A5257 (ARDENT), a large, randomized, open-label trial compared ATV/r to DRV/r or raltegravir (RAL) over 96 weeks, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events.[10]

- The DRIVE-FORWARD study compared DRV/r to doravine (DOR), both administered with two investigator-selected NRTIs, in 769 ART-naive participants. At 48 weeks, DOR was found to be noninferior to DRV/r, with 80% of participants who received DOR and 84% of participants who received DRV/r achieving HIV RNA levels <50 copies/mL.[11] At Week 96, DOR was superior to DRV/r in terms of virologic suppression (73% vs. 66%).[11] 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 occurred in 2 of 383 (1%) participants in the DOR group and 1 of 383 (<1%) participants in the DRV/r group.

Adverse Effects

- Patients taking 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 with fever or elevated transaminases occur.
- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. Bone mineral density (BMD) decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[10] 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 ($P \leq 0.02$).[12]
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease when compared to ATV/r.[5]

Other Factors and Considerations

- DRV/r is administered once daily with food in treatment-naive patients.
- DRV has a sulfonamide moiety and should be used with caution in patients 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 patients with sulfonamide allergy can tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, which may lead to significant interactions with other medications metabolized through this same pathway (see Drug–Drug Interactions).

The Panel's Recommendations

- On the basis of efficacy and safety data from clinical trials and clinical experience, the Panel classifies DRV/r with tenofovir alafenamide (TAF) or TDF with FTC or lamivudine (3TC) **(AI),** or with abacavir (ABC)/3TC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.

Darunavir/Cobicistat (DRV/c)

Efficacy in Clinical Trials

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the single-tablet regimen (STR) DRV/c/TAF/FTC with DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of

the study (91% and 88% had HIV RNA <50 copies/mL, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group.[13] At 96 weeks, 85% of participants on the STR maintained HIV RNA levels <50 copies/mL.[14]

- The DIAMOND study evaluated DRV/c/TAF/FTC as an STR in 109 patients in a rapid-initiation model of care. At Week 48, 97 (89%) participants completed the study and 92 (84%) achieved HIV-1 RNA <50 copies/mL by the FDA snapshot analysis. No protocol-defined virologic failures occurred, and incidences of adverse events and adverse drug reactions (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. [15]

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 second and third trimesters of pregnancy, and should be avoided if possible.[16] However, if pregnant women with viral suppression while on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended.

The Panel's Recommendations

- The Panel recommends DRV/c plus TAF/FTC or TDF/FTC **(AI)** and DRV/c plus ABC/3TC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- DRV/c plus TDF/FTC **is not recommended** for patients with creatinine clearance (CrCl) <70 mL/min, whereas DRV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

Atazanavir/Ritonavir (ATV/r) or Atazanavir/Cobicistat (ATV/c)

Efficacy in Clinical Trials

ATV/r plus Two NRTIs versus LPV/r plus Two NRTIs

- The CASTLE study compared once-daily ATV/r (300 mg/100 mg) with twice-daily LPV/r (400 mg/100 mg), each administered in combination with TDF/FTC. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 96 weeks.[17]

ATV/r plus Two NRTIs versus EFV plus Two NRTIs

- The ACTG A5202 study compared open-label ATV/r and efavirenz (EFV), each given in combination with placebo-controlled TDF/FTC or ABC/3TC. Efficacy was similar in the ATV/r and EFV groups.[18] In a separate analysis, women assigned to receive ATV/r were found to have a

higher risk of virologic failure than women assigned to receive EFV or men assigned to receive ATV/r.[19]

ATV/r plus Two NRTIs versus INSTI plus Two NRTIs

- In a study that compared ATV/r plus TDF/FTC to elvitegravir/cobicistat (EVG/c)/TDF/FTC, virologic suppression rates through 144 weeks were similar among participants in the two groups.[20] A Phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.[21] At Week 48, the virologic suppression rate in the EVG/c arm was superior to that in the ATV/r arm. Nineteen women in the PI arm and five women in the INSTI arm discontinued therapy because of an adverse event.
- In a Phase 3 trial, 499 ART-naive women were randomized to receive either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, the rate of virologic suppression (HIV RNA <50 copies/mL) in the DTG arm was noninferior to that in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.[22]

ATV/r plus Two NRTIs versus DRV/r plus Two NRTIs versus RAL plus Two NRTIs

- ACTG A5257 (ARDENT) was a large, randomized, open-label trial that compared ATV/r to DRV/r or RAL over 96 weeks, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events, mostly elevated indirect bilirubin/jaundice, or gastrointestinal toxicities. Lipid changes in participants in the ATV/r and DRV/r arms were similar. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[10]

ATV/c versus ATV/r plus Two NRTIs

- In the Gilead Study 114, all patients received TDF/FTC and ATV and were randomized to receive either RTV or COBI as PK enhancers. Both RTV and COBI were given as a separate tablet with matching placebos.[23] Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentages of adverse events that caused patients to discontinue treatment and changes in serum creatinine and indirect bilirubin levels also were comparable.[24]

Adverse Effects

- The main adverse effect associated with ATV/c or ATV/r is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The risk for treatment-limiting indirect hyperbilirubinemia is greatest for patients who carry two UGT1A1 decreased-function alleles.[25]
- Nephrolithiasis,[26-28] nephrotoxicity,[29] and cholelithiasis[30] also have been reported in patients who received ATV.
- Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhea.

Other Factors and Considerations

- ATV/c and ATV/r are dosed once daily with food.

- ATV requires acidic gastric pH for dissolution. As a result, concomitant use of drugs that raise gastric pH (e.g., antacids, H2 antagonists, and particularly proton pump inhibitors) may impair absorption of ATV. Table 24a provides recommendations for use of ATV/c or ATV/r with these agents.
- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see Drug–Drug Interactions).
- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[2-5] Another observational study of a cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens than in participants receiving other regimens.[6]

The Panel's Recommendations

- Based on clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus (TAF or TDF) with (FTC or 3TC) **(BI)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, and ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.
- COBI should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. However, if pregnant women with suppressed virus on ATV/c elect to continue the drug, frequent viral load monitoring is recommended.

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Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

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Reviewed: June 3, 2021

Most currently recommended antiretroviral (ARV) regimens consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third active drug. In some clinical situations, it is preferable to avoid abacavir (ABC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF), such as in patients who are HLA-B*5701 positive or at high risk of cardiovascular disease and with significant renal impairment. In this situation, dolutegravir/lamivudine (DTG/3TC), which is recommended for most people with HIV, is the preferred option. In addition, several other NRTI-limiting two-drug regimens have been evaluated in clinical studies. Of note, two-drug regimens **should not be used** in people with hepatitis B virus(HBV)/HIV coinfection or during pregnancy. Clinicians should refer to HBV/HIV Coinfection for guidance on treatment of patients 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 (DTG/3TC)

- 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 DTG plus 3TC or DTG plus TDF/emtricitabine (FTC). At week 96, DTG plus 3TC was noninferior to DTG plus TDF/FTC based on the proportion of participants with viral loads <50 copies/mL (86% in DTG plus 3TC group and 89.5% in DTG plus TDF/FTC group).[1] Virologic nonresponse was uncommon, occurring in 3.1% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No instances of treatment-emergent NRTI or integrase strand transfer inhibitor (INSTI) resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the proportion of participants with HIV RNA <50 copies/mL at week 96 was lower in the DTG plus 3TC group than in the DTG plus TDF/FTC group; however, the difference was not related to a higher rate of virologic failures in the two-drug group. At week 144, DTG plus 3TC maintained noninferiority to DTG plus TDF/FTC with 82% vs 84% of participants maintaining viral load <50 copies/ mL, respectively. The proportion of participants with viral loads ≥50 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% CI: 0.64 to 0.95).[1]
- Clinicians should refer to the INSTI section for a review of the recent data on DTG use during conception and risk of neural tube defects in infants. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential, to allow them to make an informed decision.

The Panel's Recommendation

- The Panel recommends DTG/3TC as an initial regimen for most people with HIV **(AI)**; as such, this is the preferred regimen when use of ABC, TAF, or TDF is not optimal. DTG/3TC **is not recommended:**
  - for individuals with HIV RNA >500,000 copies/mL,
  - for patients with HBV/HIV coinfection, or
  - when antiretroviral therapy (ART) is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Darunavir/Ritonavir plus Lamivudine (DRV/r plus 3TC)

- In the ANDES trial, 145 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. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies, and 24% of participants had HIV RNA >100,000 copies/mL. At week 48, 93% of the participants in the dual-therapy group and 94% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL; dual therapy was noninferior to triple therapy.[2] The rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (91% and 92%, respectively).

The Panel's Recommendation

- On the basis of results from a small study with a relatively short follow-up period, DRV/r plus 3TC can be considered for use in people who cannot take ABC, TAF, or TDF **(CI)**. Although the ANDES trial supports the use of DRV/r plus 3TC, it is a small trial of NRTI-limiting regimens, and larger studies are warranted.

Darunavir/Ritonavir plus Raltegravir (DRV/r plus RAL)

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily RAL or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the primary endpoint of proportion of patients with virologic or clinical failure. Among those with baseline CD4 counts <200 cells/mm^3, however, there were more virologic failures in the RAL + DRV/r arm; a trend towards more failure was also observed among those with pretreatment HIV RNA ≥100,000 copies/mL.[3] High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.[4, 5]

The Panel's Recommendation

- On the basis of these study results, the Panel recommends that DRV/r plus RAL be considered for use only in patients with HIV RNA <100,000 copies/mL and CD4 counts >200 cells/mm^3, and only in those patients who cannot take ABC, TAF, or TDF **(CI).**

A Nucleoside-Limiting Regimen with Insufficient Supporting Data

Darunavir/Ritonavir plus Rilpivirine (DRV/r plus RPV)

- In a single-arm, open-label, pilot study, 36 ART-naive participants without genotypic evidence of resistance to DRV or RPV received DRV/r plus RPV for 48 weeks. Half of the participants (18 of 36) had baseline HIV viral loads >100,000 copies/ml. By week 36, 97% of participants (35 of 36) achieved HIV RNA <50 copies/ml, and by week 48, all achieved viral suppression (HIV RNA <50 copies/ml).[6]

The Panel's Recommendation

- At this time, the Panel **does not recommend** DRV/r plus RPV 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.

Cabotegravir with Rilpivirine (CAB plus RPV)

The combination of cabotegravir (CAB) and RPV has not been studied in ART-naïve patients. In the Phase 3 trial FLAIR and Phase IIb trial LATTE-2,[7, 8] ART-naïve participants were first treated with 20 weeks of DTG/ABC/3TC or oral CAB+ABC/3TC, respectively, and, if they achieved virologic suppression, were eligible for randomization to receive long acting injectable CAB plus RPV every month or to continue oral daily ART. Neither CAB nor RPV is active against hepatitis B, therefore should not be used in persons with hepatitis B infection without the addition of treatment for hepatitis B. There are insufficient data for this regimen in pregnancy or around the time of conception.

The Panel's Recommendation

- The Panel **does not recommend** CAB/RPV as initial therapy for people with HIV because of the lack of data supporting the efficacy of this combination in ART-naïve patients **(AIII)**. Patients desiring to use injectable CAB plus RPV early in their treatment history should first attain viral suppression on a recommended regimen, then transition to a month of oral CAB and RPV with maintenance of suppression before transitioning to injectable CAB plus RPV. See the Optimizing Regimens section for 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 Recommended as Initial Antiretroviral Therapy

Updated: June 3, 2021
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Note: All drugs within an ARV class are listed in alphabetical order.

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 patients who test positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with BIC, DRV/c, EVG/c, or RPV • Active against HBV; a recommended dual-NRTI option for patients with HBV/HIV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC • Approved for patients with eGFR ≥30 mL/min • Can be used in patients with eGFR <30 mL/min and on chronic hemodialysis	• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. • See discussion in text regarding weight gain with TAF.
	TDF/3TC	• Coformulated with DOR • Generic formulations are available for TDF, 3TC, TDF/3TC, and EFV/TDF/3TC. • Long-term clinical experience • Active against HBV	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with lower lipid levels than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
Single NRTI	3TC	• Coformulated with DTG as STR • Avoids potential toxicities associated with TDF, TAF, ABC	• DTG/3TC is not recommended for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
INSTI	BIC	• Coformulated with TAF/FTC • Higher barrier to resistance than EVG and RAL • No food requirement	• Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • Inhibits tubular secretion of Cr without affecting glomerular function. • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug–drug interactions. • Should not be used in pregnancy because of lack of data for BIC. • See discussion in text regarding weight gain related to INSTIs.
	DTG	• Higher barrier to resistance than EVG or RAL • Coformulated with ABC/3TC and 3TC • No food requirement • Minimal CYP3A4 interactions • Favorable lipid profile	• Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
			• UGT1A1 substrate; potential for drug interactions (see Table 24d). • Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs. • Updated data from Botswana suggest that DTG exposure during conception may be associated with a small risk of NTDs in the infant compared with non-DTG ARV drugs (1.9 per 1,000 versus 1.1 per 1,000), with a prevalence difference that was not statistically significant. Clinicians should discuss with people of childbearing potential and refer to the Perinatal Guidelines.
	EVG/c	• Coformulated with TDF/FTC or TAF/FTC • Compared with ATV/r, EVG/c causes smaller increases in total and LDL cholesterol. • EVG/c/TAF/FTC can be used in patients on chronic hemodialysis.	• EVG/c/TDF/FTC is recommended only for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min. • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • Oral absorption of EVG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Food requirement. • Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions). • EVG/c should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on EVG/c elect to continue on the drug, frequent viral load monitoring is recommended. • See discussion in text regarding weight gain related to INSTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
	RAL	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions • Favorable lipid profile	• Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe HSRs (including SJS and TEN) have been reported. • Higher pill burden than other INSTI-based regimens. • No FDC formulation. • Oral absorption of RAL can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals). See dosing recommendations in Table 24d. • UGT1A1 substrate; potential for drug interactions (see Table 24d). • Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs.
NNRTI	DOR	• Coformulated with TDF/3TC • Compared to EFV, fewer CNS side effects • No food requirement • Favorable lipid profile • Lack of association with weight gain compared with boosted DRV or EFV	• Shorter-term clinical experience than with EFV and RPV. • Potential for CYP450 drug interactions (see Tables 24b, 25a and 25b). • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.
	EFV	• EFV 600 mg is coformulated with TDF/FTC and TDF/3TC. • EFV 400 mg is coformulated with TDF/3TC. • EFV 600-mg dose has long-term clinical experience and EFV-based regimens (except for EFV plus ABC/3TC) have well-documented efficacy in patients with high HIV RNA.	• Short- and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality and catatonia. Late-onset ataxia and encephalopathy also have been reported. • Periodic screening for depression and suicidality is recommended in people with HIV who are taking a regimen that includes EFV. • Dyslipidemia • Rash

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
		• EFV 400 mg has fewer CNS side effects than EFV 600 mg. • EFV 600 mg can be given with rifamycin antibiotics (rifampin, rifabutin, or rifapentine).	• QTc interval prolongation; consider using an alternative to EFV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes. • Transmitted resistance is more common than with PIs and INSTIs. • Greater risk of resistance at the time of treatment failure than with PIs. • Potential for CYP450 drug interactions (see Tables 24b and 25a). • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities).
	RPV	• Coformulated with TDF/FTC and TAF/FTC • RPV/TDF/FTC and RPV/TAF/FTC have smaller pill sizes than other coformulated ARV drugs • Compared with EFV: o Fewer CNS adverse effects o Fewer lipid effects o Fewer rashes	• Not recommended in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3 because of higher rate of virologic failure in these patients. • Depression and suicidality • QTc interval prolongation; consider using an alternative to RPV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes. • Rash • Transmitted resistance is more common than with PIs and INSTIs. • More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs. • Potential for CYP450 drug interactions (see Tables 24b and 25a). • Meal requirement (>390 kcal) • Requires acid for adequate absorption. o Contraindicated with PPIs. o Use with H2 antagonists or antacids with caution (see Table 24a for detailed dosing information).

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
PIs	ATV/c or ATV/r	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs. • ATV/c and ATV/r have similar virologic activity and toxicity profiles. • Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events; this risk has not been seen with ATV. Further study is needed. See text for discussion. • Individual ATV and RTV components are available as generics.	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice. • Food requirement • Absorption depends on food and low gastric pH (see Table 24a for interactions with H2 antagonists, antacids, and PPIs). • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 24a).
	ATV/c Specific considerations	Coformulated tablet	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF is not recommended in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on ATV/c elect to continue on the drug, frequent viral load monitoring is recommended.
	DRV/c or DRV/r	• Higher barrier to resistance than NNRTIs, EVG, and RAL. • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs.	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 24a). • Increased CV risk reported in one observational cohort study. • Hepatotoxicity has been reported, especially in those with preexisting liver disease.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
	DRV/c Specific considerations	• Coformulated as DRV/c and DRV/c/TAF/FTC.	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF is not recommended in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI should be avoided in pregnancy, because levels of COBI and its boosted drugs are lower in the second and third trimesters. If women who are pregnant with suppressed virus on DRV/c elect to continue on the drug, frequent viral load monitoring is recommended.

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; UGT = uridine diphosphate glucuronosyltransferase

Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy

Updated: June 3, 2021
Reviewed: June 3, 2021

ARV Components or Regimens	Reasons for *Not* Recommending as Initial Therapy
Combination INSTI plus NNRTI	
CAB plus RPV (PO or IM)	• This regimen only is approved for people who have achieved viral suppression on another ARV regimen. It has not been studied as initial ARV regimen.
DTG plus RPV	• This regimen only is approved for people who have achieved viral suppression on another ARV regimen. It has not been studied as initial ARV regimen.
NRTIs	
ABC/3TC/ZDV (Coformulated) As triple-NRTI combination regimen	• Inferior virologic efficacy
ABC/3TC/ZDV plus TDF As quadruple-NRTI combination regimen	• Inferior virologic efficacy
d4T plus 3TC	• Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)
ddI plus 3TC (or FTC)	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicities, such as pancreatitis and peripheral neuropathy
ddI plus TDF	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 cell decline • Increased ddI drug exposure and toxicities
ZDV/3TC	• Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs
NNRTIs	
DLV	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ETR	• Insufficient data in ART-naive patients
NVP	• Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including SJS and TEN) • When compared to EFV, NVP did not meet noninferiority criteria

ARV Components or Regimens	Reasons for *Not* Recommending as Initial Therapy
PIs	
ATV (Unboosted)	• Less potent than boosted ATV
DRV (Unboosted)	• Use without RTV or COBI has not been studied
FPV (Unboosted) or FPV/r	• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV • Less clinical trial data for FPV/r than for other RTV-boosted PIs
IDV (Unboosted)	• Inconvenient dosing (3 times daily with meal restrictions) • Fluid requirement • IDV toxicities, such as nephrolithiasis and crystalluria
IDV/r	• Fluid requirement • IDV toxicities, such as nephrolithiasis and crystalluria
LPV/r	• Higher pill burden than other PI-based regimens • Higher RTV dose than other PI-based regimens • GI intolerance
NFV	• Inferior virologic efficacy • Diarrhea
RTV as sole PI	• High pill burden • GI intolerance • Metabolic toxicity
SQV (Unboosted)	• Inadequate bioavailability • Inferior virologic efficacy
SQV/r	• High pill burden • Can cause QT and PR prolongation; requires pretreatment and follow-up ECG
TPV/r	• Inferior virologic efficacy • Higher rate of adverse events than other RTV-boosted PIs • Higher dose of RTV required for boosting than other RTV-boosted PIs
Entry Inhibitors	
FTR gp120 Attachment Inhibitor	• Only studied in a very small number of patients with virologic failure
IBA CD4 Post-Attachment Inhibitor	• Only studied in a very small number of patients with virologic failure • Requires IV therapy • High cost

ARV Components or Regimens	Reasons for *Not* Recommending as Initial Therapy
MVC CCR5 Antagonist	• Requires testing for CCR5 tropism before initiation of therapy • No virologic benefit when compared with other recommended regimens • Requires twice-daily dosing
T20 Fusion Inhibitor	• Only studied in patients with virologic failure • Twice-daily subcutaneous injections • High rate of injection site reactions

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CAB = cabotegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; IM = intramuscular; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = oral; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

What Not to Use

Updated: October 17, 2017
Reviewed: October 17, 2017

Some antiretroviral (ARV) regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

Antiretroviral Drugs Not Recommended

The following ARV drugs are no longer recommended for use because of suboptimal antiviral potency, unacceptable toxicities, high pill burden, or pharmacologic concerns: delavirdine (DLV), didanosine (ddI), indinavir (IDV), nelfinavir (NFV), and stavudine (d4T).

Antiretroviral Regimens Not Recommended

Monotherapy

Nucleoside reverse transcriptase inhibitor (NRTI) monotherapy is inferior to dual-NRTI therapy.[1] Protease inhibitor (PI) monotherapy is inferior to combination antiretroviral therapy (ART).[2-6] Integrase strand transfer inhibitor (INSTI) monotherapy has resulted in virologic rebound and INSTI resistance **(AI).**[7,8]

Dual-NRTI Regimens

These regimens are inferior to triple-drug combination regimens **(AI).**[9]

Triple-NRTI Regimens

Triple-NRTI regimens have suboptimal virologic activity[10-12] or a lack of data **(AI).**

Antiretroviral Components Not Recommended

Atazanavir plus Indinavir

Both PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly **(AIII).**

Cobicistat plus Ritonavir as Pharmacokinetic Enhancers

This combination may be prescribed inadvertently, which may result in additive CYP3A4 enzyme inhibition and may further increase the concentrations of ARV drugs or other concomitant medications (see Tables 24a and 24d).

Didanosine plus Stavudine

The combination of ddI and d4T can result in peripheral neuropathy, pancreatitis, and lactic acidosis, and it has been implicated in the deaths of several pregnant women **(AII).**[13]

Didanosine plus Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) increases ddI concentrations,[14] serious ddI-associated toxicities,[15,16] immunologic nonresponse,[17] early virologic failure,[18,19] and resistance[18,20] **(AII).**

Two Non-Nucleoside Reverse Transcriptase Inhibitor Combinations

Excess clinical adverse events and treatment discontinuation were reported in patients randomized to receive treatment with two non-nucleoside reverse transcriptase inhibitors (NNRTIs).[21] Efavirenz (EFV) and nevirapine (NVP) are enzyme inducers, and both of these drugs can reduce concentrations of etravirine (ETR) and rilpivirine (RPV) **(AI).**[22]

Emtricitabine plus Lamivudine

Both drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo* **(AIII).**[23]

Etravirine plus Unboosted Protease Inhibitor

ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established **(AII).**[22]

Etravirine plus Fosamprenavir/Ritonavir

ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established **(AII).**[22]

Etravirine plus Tipranavir/Ritonavir

Tipranavir/ritonavir (TPV/r) significantly reduces ETR concentrations **(AII).**[22]

Nevirapine Initiated in ARV-Naive Women with CD4 Counts >250 cells/mm^3 or in ARV-Naive Men with CD4 Counts >400 cells/mm^3

Initiating NVP in ART-naive individuals with CD4 counts above these thresholds increases the risk of symptomatic, and sometimes life-threatening, hepatic events.[24-26] ART-experienced patients can safely switch to NVP if they have CD4 counts above these thresholds as a result of receiving effective ART **(BI).**[27]

Unboosted Darunavir, Saquinavir, or Tipranavir

The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV, or in the case of DRV, also with COBI **(AII).**

Stavudine plus Zidovudine

These NRTIs are antagonistic *in vitro*[28] and *in vivo*[29] **(AII).**

Tenofovir Alafenamide plus Tenofovir Disoproxil Fumarate

This combination may be prescribed inadvertently, especially during transition from one formulation to another. There is no data supporting any potential additive efficacy or toxicity if TAF and TDF are used in combination.

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Management of the Treatment-Experienced Patient

Virologic Failure

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Key Considerations and Recommendations
• Assessing and managing a patient 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 patient is taking the failing antiretroviral (ARV) regimen (AI) or within 4 weeks of treatment discontinuation of 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. • The goal of treatment for ART-experienced patients 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 regimen can include two fully active ARV drugs if at least one with a high resistance barrier is included (e.g., dolutegravir or boosted darunavir) (AI). If no fully active drug with a high resistance barrier is available, then every effort should be made to include three fully active drugs (AI). • In general, adding a single ARV drug to a virologically failing regimen is not recommended, because this would rarely result in full viral suppression and, therefore, may risk the development of resistance to all drugs in the regimen (BII). • For some rare highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. 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 patient with multidrug-resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available. • In patients with virologic failure, it is crucial to provide continuous adherence support before and after ARV regimen changes. • When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, the patient should remain on an ARV agent that is active against HBV and has a high resistance barrier to HBV in order to avoid HBV rebound and hepatocellular damage. • 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, this strategy 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 patients 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 What to Start). Patients 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 regimen. Adherence to ARV regimens can be challenging for some patients, and poor adherence can result in detectable viral loads. Depending on their ARV treatment histories, some of these patients may have minimal or no drug resistance and others may have extensive resistance. Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in patients 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 patient who has not yet had documented virologic suppression on that regimen. A patient'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 detectable HIV-RNA level <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 patients 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 patients 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 viral load platforms used in the past.[3-5] Several retrospective studies support the supposition that virologic failure is more likely to occur in patients with viral load ≥200 copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.[6,7]

However, other studies have suggested that detectable viremia at this level (<200 copies/mL) can be predictive of virologic failure[8,9] and can be associated with the evolution of drug resistance.[10]

Persistent HIV-RNA level ≥200 copies/mL is often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[11] This association is particularly common when HIV-RNA level is >500 copies/mL.[12] Therefore, patients who have persistent HIV-RNA level ≥200 copies/mL are considered to be experiencing virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from patient 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.[13,14] The presence of preexisting (transmitted) drug resistance also may lead to virologic failure.[15] Virologic failure may be associated with a variety of factors, including the following:

Patient/Adherence-Related Factors (see Adherence to the Continuum of Care)

- Comorbidities that may affect adherence (e.g., active substance use, mental health disorders, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of, or intermittent access to, ART
- Cost and affordability of ARV drugs (i.e., factors that may affect the ability to access or continue therapy)
- Adverse drug effects
- High pill burden and/or dosing frequency

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 level (some regimens may be less effective at higher levels)

Antiretroviral Regimen-Related Factors

- Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism, or 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
- Prescription (prescribing or dispensing) errors

Managing Patients with 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. Often, the causes of virologic failure can be identified, but in some cases, they are not obvious. 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. Approaches to designing a new ARV regimen are outlined below.

Key Factors to Consider When Designing an Antiretroviral Regimen After Virologic Failure

General Principles on Antiretroviral Use in Virologic Failure

- When designing a new ARV regimen for a patient with virologic failure, it is important to consider the factors outlined above on causes of virologic failure (including medication potency) and, if possible, consider well-tolerated and adherence-friendly regimens.
- A new regimen should be selected based on the patient's ART history, a review of their current and previous drug-resistance test results, and whether a fully susceptible ARV drug with high barrier to resistance and other fully active drugs are available.[8,16-28]
- ARV agents with high barrier to resistance are those in which emergent resistance is uncommon in patients experiencing virologic failure, and these include boosted darunavir (DRV), dolutegravir (DTG), and bictegravir (BIC).
- Fully active drugs may include—
  - Drugs in classes for which the patient has not previously selected for drug-resistant virus.
  - Newer members of existing drug classes—which despite the presence of resistant mutations to some drugs in that class are predicted to be fully active against HIV isolates—such as 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 which the patient has not received before, such as the post-attachment inhibitor ibalizumab (IBA), the gp120-attachment inhibitor fostemsavir (FTR), the fusion inhibitor enfuvirtide (T-20), or the CCR5 antagonist maraviroc (MVC) in patients 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 patient 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 patient with overt or low-level viremia **is not recommended,** because it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count, and it increases the risk of clinical progression **(AI)**[29,30] (see Discontinuation or Interruption of Antiretroviral Therapy).

Drug-Resistance Testing to Guide New Antiretroviral Regimens

- Drug-resistance testing should guide ARV regimen design and should be performed while the patient is still taking the failing regimen 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 virologic failure and HIV RNA >200 copies/mL **(AI** for >1,000 copies/mL, **AIII** for 501–1,000 copies/mL, **CIII** for confirmed 201–500 copies/mL**);** though at low viral load 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 patient'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 a patient'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 PIs; INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in patients who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for patients who experience failure on a fusion inhibitor **(AII),** and viral tropism tests for patients who experience failure on a CCR5 antagonist **(BIII)** also are available. There is currently no commercially available resistance test for IBA or FTR (see Drug-Resistance Testing).

Strategies for New Antiretroviral Regimen Design

- A new ARV regimen can include two fully active drugs if at least one has a high resistance barrier, such as the second-generation INSTI DTG or the boosted-PI DRV **(AI).**[31-39]
- A new ARV regimen can include an INSTI (preferably the second-generation DTG) plus boosted PI (preferably boosted DRV), without NRTIs, if both are fully active **(AII);** this is discussed in more detail below.[33,34,38,39]

- 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 patient'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 patients with relevant resistance mutations to achieve drug concentrations necessary to be at least partially active against a less-sensitive virus.[40-42]
- In contrast, other agents in which resistance may be expected should be discontinued, because their continued use is unlikely to contribute to viral suppression. These drugs may include NNRTIs, especially efavirenz, nevirapine, and rilpivirine (RPV); the first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG); and T-20.[43-45]
- The long-acting ARV combination of injectable cabotegravir (CAB) and RPV is **not currently recommended** for people with virologic failure.
- When changing an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV (especially tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) should be continued as part of the new regimen or, if not possible, entecavir should be initiated **(BI).** Using lamivudine (3TC) or emtricitabine (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).
- Patients should be closely monitored for virologic responses after regimen switch (e.g., HIV viral load testing performed within 4 to 8 weeks), with prompt drug-resistance testing if virologic response is inadequate.

Managing Virologic Failure in Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogenous 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 for all patients with detectable viral loads 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 level of viremia are addressed below.

- **Low-level viremia (HIV RNA above the LLOD and <200 copies/mL):** Patients 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 patients, the risk that drug resistance will emerge is believed to be relatively low. Therefore, these patients 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 patients with detectable HIV-RNA levels that are persistently <200 copies/mL, those with levels that are persistently ≥200 copies/mL often develop drug resistance, particularly when HIV-RNA levels are >500 copies/mL.[6,7] Patients 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 patients with HIV-RNA levels >500 copies/mL. Management approaches should be the same as for patients 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 determine 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). Approaches include the following:
    - Assessing the patient'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 the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind 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 patient 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 and dietary supplements for possible adverse drug–drug interactions (consult Drug–Drug Interactions and Tables 24a through 25b for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
    - Considering therapeutic drug monitoring if PK drug–drug interactions (e.g., when used with rifamycin) or impaired drug absorption (e.g., using polyvalent cations with an INSTI) leading to decreased ARV drug exposure is suspected.
    - Considering the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for >4 weeks before testing?) (see Drug-Resistance Testing).
        - 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.
  - Viral load testing should be repeated 4 to 8 weeks after treatment adherence is reinforced or treatment is modified **(AII);** if viral load remains >200 copies/mL, genotypic 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 viral load 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.[46] 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.[8,47] 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 of these patients. 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

See Table 11 below for a summary of these recommendations.

Virologic Failure on the First Antiretroviral Regimen

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that drug-resistance testing should be used 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, patients 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.

- **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).** 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 **(BII).** BIC, which is available only in a combination pill with FTC/TAF, also has a high resistance barrier and may have activity that is similar to that of DTG in this setting; however, no clinical trial data for this strategy is available and, therefore, it **is not currently recommended (CIII).**

  In the DAWNING trial, patients 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 patients in the DTG arm selected for INSTI resistance, with no PI resistance selected for in the LPV/r arm.[37]

In the NADIA trial, participants in Uganda, Kenya, and Zimbabwe who experienced virologic failure while on a first-line NNRTI plus 3TC or FTC with TDF regimen were randomized to receive either darunavir/ritonavir (DRV/r) or DTG, each with 3TC; participants were assigned by a second randomization to receive 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.[35,36] The primary study outcome was viral suppression <400 copies/mL: at 48 and 96 weeks, >85% of participants had viral load <400 copies/mL in all arms, and the DTG-based regimens were noninferior to the DRV/r-based regimens. However, at 96 weeks, 9 of 235 (4%) participants in the DTG group developed DTG resistance. This represented 45% of participants in the DTG group with viral load >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 viral 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 viral 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 in a public health approach, ZDV should not be used over tenofovir. The decision to use DTG or DRV/r without another fully active drug should balance the overall efficacy data of these regimens, with considerations to the potential for emerging 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 patient populations outside of the trials due to differences in geography, patient 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 **(BII).** Notably, boosted PIs as monotherapy **are not recommended (AI).**[33-36,39,48]

  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 were noninferior at 48 and 96 weeks, with TDF being noninferior 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 viral 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, these results should be interpreted with caution within, and particularly beyond, the study patient populations and settings.

- **Boosted PI plus an INSTI:** As noted earlier, a regimen that consisted of LPV/r plus RAL was found to be as effective as LPV/r plus at least two NRTIs.[33,34,39] Thus, LPV/r plus RAL can be a treatment option for those who experienced virologic failure on an NNRTI-based regimen **(CI).** Although data are limited, a boosted PI (e.g., DRV) that is a preferred option combined with DTG would be a viable option in this setting **(AIII).**

Boosted PI plus NRTI regimen failure: In this scenario, because boosted PI has a high barrier to resistance, most patients will have either no resistance or resistance that is limited to 3TC and FTC; though additional NRTI mutations also may be present.[49,50] Failure in this setting is often attributed to poor adherence, drug–drug interactions, or drug–food interactions. Below are some management options.

- **Switch to an INSTI-based regimen:** Second-generation INSTIs have increasingly become preferred options over boosted PIs due to the lack of drug–drug interactions, 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 (particularly TAF or TDF with 3TC or FTC) can be considered **(BIII).** As outlined above, 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 patient populations outside of the trials, due to differences in geography, 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 PI/r-based regimens showed that maintaining the same regimen while making efforts to enhance adherence is as effective as changing to new regimens with or without drugs from new classes **(AII).**[51] 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 an INSTI-based regimen 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 an 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 **(BIII).**

INSTI plus NRTI regimen failure: Virologic failure in patients 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.[52] Viruses with EVG or RAL resistance often remain susceptible to DTG and BIC.[47] However, in the presence of certain INSTI mutations, DTG dose should be increased from once daily to twice daily.[40] 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.[52-54] 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 patient 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.**

INSTI plus NNRTI regimen failure: Virologic failure in patients 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.[55,56] 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 antiretroviral therapy options: Using a patient'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, patients 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, viral 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 patient's treatment history, past and present drug-resistance testing, and tropism testing if a CCR5 antagonist is being considered.

Multidrug resistance without fully active antiretroviral therapy options: Use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have few treatment options because of multiclass drug-resistance.[57,58] Despite this progress, some patients have experienced toxicities with and/or developed resistance to most currently available 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 these patients 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, 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.[57,59] 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.[60] Other cohort studies suggest that even modest reductions in HIV-RNA levels continue to confer immunologic and clinical benefits.[61,62] 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).**

Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for the first-in-class CD4 post-attachment inhibitor IBA[63] and/or the gp120-directed attachment inhibitor FTR.

- **IBA:** 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 infusions of IBA every 2 weeks, in addition to an optimized background regimen 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% of participants achieved HIV RNA <200 copies/mL.[64] 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 patients who had HIV RNA <50 copies/mL at Week 24 maintained viral suppression up to Week 48.[65]
- **FTR:** 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 optimized background ART. In the nonrandomized cohort (n = 99), participants with no remaining ARV options were started on open-label FTR (oral 600 mg twice daily) plus optimized background ART on Day 1. The primary endpoint for the randomized cohort was change in viral load from baseline at Day 8. In

the FTR group, the mean viral load decrease was 0.79 $\log_{10}$ copies/mL versus 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 viral load <40 copies/mL, with mean CD4 increases of 205 cells/mm^3 and 119 cells/mm^3, respectively.[66,67] 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.

Patients 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-patient access to an investigational new drug as specified in the U.S. Food and Drug Administration regulations. Information about ARV agents that are in clinical studies (e.g., lenacapavir) can be found in the drug database available on the *Clinical Info* website.

Antiretroviral Therapy-Experienced Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Drug-Resistance Test Results)

Every effort should be made to obtain the patient'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 patient'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/or boosted DRV—as part of the regimen. Regardless of which strategy is employed, patients should be closely monitored for virologic response (e.g., HIV viral load testing approximately 4 to 8 weeks after re-initiation of therapy), with prompt drug-resistance testing performed if virologic response is inadequate.

Summary

The goal of treatment for ART-experienced patients with virologic failure is to establish virologic suppression. The management of ART-experienced patients 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 11. Antiretroviral Options for Patients with Virologic Failure

Designing a new regimen for patients 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 patients 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 to all patients before and after regimen changes.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/– 3TC or FTC (i.e., NNRTI mutations +/– M184V/I).[c] Additional NRTI mutations also may be present.	DTG (or possibly BIC) plus two NRTIs (preferably at least one fully active*) (AI); *or* Boosted PI plus two NRTIs (preferably at least one fully active) (AI); *or* Boosted PI plus INSTI (CI or AIII)[d]	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)[c]	DTG, or possibly BIC, plus two NRTIs (preferably at least one fully active; if only one of the NRTIs is fully active* or if adherence is a concern, DTG is currently preferred over other INSTIs) (AIII); *or* Continue same regimen (AII); *or* Another boosted PI plus INSTI (CI or AIII)[d]; *or* Another boosted PI plus two NRTIs (at least one fully active*) (AIII)	Resuppression
	INSTI plus two NRTIs	If failure on DTG or BIC, typically no INSTI resistance; Can have 3TC or FTC resistance (i.e., only M184V/I, usually without resistance to other NRTIs)[c]	Boosted PI plus two NRTIs (preferably at least one fully active*) (AIII); *or* DTG, or likely BIC, plus two NRTIs (preferably at least one fully active*) (AIII); *or* Boosted PI plus DTG (AIII)	Resuppression
		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*) (AIII); *or* DTG[e] twice daily or possibly BIC (if HIV is sensitive) plus two fully active NRTIs (BIII); *or*	Resuppression

Table 11. Antiretroviral Options for Patients with Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
			DTG[e] twice daily or possibly BIC (if HIV is sensitive) plus a boosted PI (AIII)	
Second Regimen Failure and Beyond	Drug resistance with fully active treatment options— (i) Boosted PI, but not second-generation INSTI, fully active (ii) Second-generation INSTI, but not boosted PI, fully active (iii) Both PI and INSTI fully active	Use past and current genotypic- +/– phenotypic-resistance testing and ART history when designing new regimen.	(i) Boosted PI with two NRTIs (preferably at least one fully active) (ii) DTG or BIC with two NRTIs (preferably at least one fully active) (iii) The two options above or boosted PI with INSTI	Resuppression
	Multiple or extensive drug resistance with few treatment options (e.g., fully active boosted PI or second-generation INSTI unavailable)	Use past and current genotypic- and phenotypic-resistance testing to guide therapy. Confirm with a viral tropism assay when use of MVC is considered. Consult an expert in drug resistance if needed.	New regimen should include at least two, and preferably three, fully active agents, including those with novel mechanisms of action (e.g., IBA or FTR). If <3 fully active drugs, include as many fully active drugs as possible, along with potentially partially active drugs. Consider enrollment into clinical trials or expanded access programs for investigational agents if available. Discontinuation of all ARV drugs is not recommended.	Resuppression if possible; otherwise, keep viral load as low as possible and CD4 count as high as possible.
ART-Experienced Patients 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 patient has been off ART. Keep in mind that resistance mutations may	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	Resuppression

Table 11. Antiretroviral Options for Patients with Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
		not be detected in the absence of drug pressure.	monitoring of virologic response and early resistance testing, if inadequate virologic suppression.	

[a] Data are insufficient to provide a recommendation for the continuation of 3TC or FTC in the presence of M184V/I.

[b] When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs that are active against HBV and have high resistance barrier to HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

[c] If other NRTI-resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

[d] CI for LPV/r + RAL; AIII for other boosted PIs (e.g., DRV) or INSTIs (e.g., DTG).

[e] Response to DTG depends on the type and number of INSTI mutations.

*See text for details and additional options in special settings.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; 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. These patients present with new, usually subacute, neurological symptoms that are associated with 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.[68-70] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging (MRI) and abnormal CSF findings with characteristic lymphocytic pleocytosis.[71] In most (though not all) patients, drug-resistant CSF virus is evident.[72] 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).**[73] 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 patient's treatment history or on predicted drug penetration into the CNS **(CIII).**[74-77]

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;[78-80] *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).[81]

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 individual patient with this condition is recommended to monitor for emergence of neurologic symptoms or systemic viremia.[73] 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 patients with HIV who show no evidence of CNS viral breakthrough.[82]

Neurological Symptoms in People with HIV on Antiretroviral Therapy

Evidence is currently not available to support empiric intensification or switch of ARV regimens in patients on systemically suppressive ART with mild neurological and/or cognitive symptoms who do not have documented CSF escape. Such patients 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 multi-national randomized, double-blinded, placebo-controlled trial randomized 191 ART-experienced participants—with cognitive impairment and suppressed plasma HIV viral load 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.[83]

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Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression

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Key Considerations and Recommendations
• Persistently low CD4 T lymphocyte (CD4) cell counts and immune activation are each associated with increased AIDS- and non-AIDS-related morbidity and mortality among individuals with antiretroviral therapy (ART)-mediated viral suppression. • Adding antiretroviral (ARV) drugs to a suppressive ARV regimen (ART intensification) does not improve CD4 cell recovery or reduce immune activation and, therefore, is not recommended (AI). • In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce all relevant markers of immune activation and is not recommended (BIII). • Interleukin-2 is not recommended (AI) to increase CD4 cell counts and/or decrease immune activation, because clinical trial data demonstrated no clinical benefit. • Other interventions designed to increase CD4 cell counts and/or decrease immune activation are not recommended outside of a clinical trial, because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression (AII). • Efforts to decrease morbidity and mortality during ART-mediated viral suppression should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and regular exercise; treating hypertension and hyperlipidemia). • Monitoring markers of immune activation and inflammation is not recommended, because no intervention targeting immune pathways has proven to improve the health of individuals with HIV, and many blood markers that predict morbidity and mortality fluctuate within individuals (AII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Despite marked improvements in antiretroviral treatment (ART), morbidity and mortality in individuals with HIV continue to be greater than in the general population, particularly when ART is delayed until advanced disease stages. These morbidities include cardiovascular disease, many non-AIDS cancers, non-AIDS infections, chronic obstructive pulmonary disease, osteoporosis, type 2 diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and the frailty phenotype.[1] Although health-related behaviors and toxicities of antiretroviral (ARV) drugs are important factors, immune characteristics, such as a poor CD4 T lymphocyte (CD4) cell recovery and persistent immune activation and inflammation, likely also contribute to the disease risk among persons with HIV.

Poor CD4 Cell Recovery

As long as ART-mediated viral suppression is maintained, peripheral blood CD4 cell counts in most individuals with HIV will continue to increase for at least a decade. The rate of CD4 cell recovery is typically most rapid in the first 3 months of suppressive ART, followed by more gradual increases over time.[2-4] If ART-mediated viral suppression is maintained, most individuals will eventually

recover CD4 counts in the normal range (>500 cells/mm^3); however, approximately 15% to 20% of individuals who initiate ART at very low CD4 counts (<200 cells/mm^3) may plateau at abnormally low CD4 cell counts.[3-5] Early initiation of ART in individuals with recent HIV diagnoses likely provides the best opportunity for maximal CD4 cell recovery.[6]

Persistently low CD4 cell counts despite ART-mediated viral suppression are associated with increased risk of morbidity and mortality. For example, individuals with HIV who have CD4 counts <200 cells/mm^3, despite at least 3 years of suppressive ART, had a 2.6-fold greater risk of mortality than those with higher CD4 cell counts.[7] Lower CD4 cell counts during ART-mediated viral suppression are associated with an increased risk of non-AIDS morbidity and mortality,[8-11] including cardiovascular disease,[12] osteoporosis and fractures,[13] liver disease,[14] and infection-related cancers.[15] The prognostic importance of higher CD4 cell counts likely spans all ranges of CD4 cell counts, though incremental benefits are harder to discern once CD4 counts increase[16] to >500 cells/mm^3.

Individuals with poor CD4 cell recovery should be evaluated for modifiable causes of CD4 cell lymphopenia. Concomitant medications should be reviewed, with a focus on those known to decrease white blood cells or, specifically, CD4 cells. If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., hepatitis C virus, HIV-2) and serious medical conditions (e.g., malignancy) also should be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and in those with CD4 counts consistently below 100 cells/mm^3.

In rare cases, CD4 cell counts actually decline, despite suppressive ART in the absence of an obvious clinical cause. Severe derangements in interleukin (IL)-7-**mediated** naive T cell homeostasis have been reported in these individuals, although the pathophysiology is likely to be multifactorial.[17-19]

Despite strong evidence linking low CD4 cell counts and increased morbidity during ART-mediated viral suppression, no adjunctive therapies that increase CD4 cell count beyond levels achievable with ART alone have been proven to decrease morbidity or mortality. Adding ARV drugs to an already suppressive ARV regimen does not improve CD4 cell recovery,[20-25] and does not reduce morbidity or mortality. Therefore, ART intensification is not recommended as a strategy to improve CD4 cell recovery **(AI).** Similarly, for individuals who are already maintaining viral suppression, switching ARV drug classes also does not consistently improve CD4 cell recovery and is not recommended **(BIII).**[26]

Immune-based therapies also have been investigated as a strategy to increase CD4 cell counts (e.g., IL-2, IL-7, growth hormone). Two large clinical outcome trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2 for improving CD4 cell recovery. IL-2 adjunctive therapy resulted in substantial CD4 cell count increases but with no observable clinical benefit.[27] Therefore, IL-2 is **not recommended (AI).** Given the lack of established clinical benefit to date, other immune-based therapies should not be used except in the context of a clinical trial.

Persistent Immune Activation and Inflammation

HIV infection results in heightened systemic immune activation and inflammation, which predict more rapid CD4 cell decline and progression to AIDS and death, independent of plasma HIV RNA levels.[28] Although immune activation declines with suppressive ART, it often persists at abnormal levels in many individuals with HIV maintaining long-term ART-mediated viral suppression—even

in those with CD4 cell recovery to normal levels.[29, 30] Immune activation and inflammatory markers (e.g., IL-6, D-dimer, high sensitivity C-reactive protein (hs-CRP) also predict mortality and non-AIDS morbidity during ART-mediated viral suppression, including cardiovascular and thromboembolic events, cancer, neurocognitive dysfunction, and frailty.[28] A low CD4/CD8 ratio also might reflect this inflammatory state to some degree,[31] although it predicts AIDS events far more strongly than non-AIDS morbidity.[32] Although individuals with poor CD4 cell recovery (i.e., counts persistently <350 cells/mm^3) tend to have greater immune activation and inflammation than those with greater recovery,[29] the relationship between innate immune activation and inflammation and morbidity/mortality is largely independent of CD4 cell count.[33, 34] Even in individuals with CD4 counts >500 cells/mm^3, immune activation and inflammation are associated with increased morbidity and mortality.[35, 36]

ART as a Strategy to Reduce Inflammation

Early diagnosis and treatment of HIV is, potentially, an effective strategy to achieve a lower level of persistent immune activation with ART. Most inflammatory markers decline during the first several months of ART and achieve a stable "setpoint" within 1 to 2 years.[37, 38] In observational studies, people with HIV who initiated ART during acute HIV infection appeared to achieve a lower immune activation setpoint during ART-mediated viral suppression than those who started ART at later disease stages.[39, 40] Indeed, those randomized to the immediate treatment arm of the START trial appeared to achieve a lower early inflammatory setpoint than those who were randomized to delayed therapy.[41] Longer-term follow-up of START participants is needed to determine whether such a reduced inflammatory setpoint persists and translates into reduced morbidity and mortality. Collectively, these data reinforce the recommendation to start ART as soon as possible after HIV diagnosis (see Initiation of Antiretroviral Therapy).

Although earlier initiation of ART appears to consistently reduce the inflammatory setpoint during ART, intensifying or modifying ART after viral suppression is already achieved does not appear to consistently reduce immune activation. For example, adding ARV drugs to an already suppressive ARV regimen (or ART intensification) does not consistently improve immune activation.[20-23, 25] Although some studies have suggested that switching an ARV regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation,[42-44] these studies have limitations and results are not consistent across markers and among studies. Thus, at this time, ART modification cannot be recommended as a strategy to reduce immune activation **(BIII).**

Other Immune-Based Strategies

Because persistent immune activation is associated with morbidity and mortality among people with HIV who are virologically suppressed with ART, strategies targeting immune-mediators of inflammation are under investigation. Although the efficacy of canakimumab is not yet proven in people with HIV, the CANTOS trial provided important proof of concept for the causal role of inflammation in the risk of multi-morbidity in people without HIV but with cardiovascular disease. The study demonstrated that treatment with canakimumab, a human monoclonal antibody targeting cytokine IL-1β, a driver of the IL-6 signaling pathway, reduced cardiovascular events and cancer death.[45] In people with HIV, canakinumab and the IL-6 inhibitor tocilizumab have been shown to reduce blood levels of markers of inflammation and immune activation.[46, 47] Nevertheless, it remains unclear whether the potential risks of these therapies, such as the increased risk of death from sepsis observed in the CANTOS trial, might outweigh any benefits in people with HIV. Therefore,

interventions targeting immune mediators of inflammation are not currently recommended for clinical use for the treatment of immune activation in people with HIV **(AII).**

Treatments Targeting Traditional Risk Factors and Inflammation

Beyond the well-established clinical benefit for reducing cardiovascular events, HMG-CoA reductase inhibitors (or statins) have been shown to improve biomarker levels of inflammation (e.g., hsCRP) and immune activation in the general population.[48-50] This premise, and the data suggesting similar benefit among people with HIV, motivated the design of a large clinical trial (REPRIEVE), now fully enrolled, to determine whether pitavastatin reduces cardiovascular events in people with HIV who do not already have a clinical indication for cholesterol-lowering therapy. [51] Although the results will not be known for several years, in addition to identifying the primary cardiovascular outcomes, assessing the impact of pivitastatin on non-cardiovascular events (such as cancer, osteoporotic fractures, and frailty phenotypes) that may be linked to the inflammatory state also will be valuable. Similarly, it remains unclear whether statins might further increase type 2 diabetes risk, which is increased in people with HIV.[52] Other commonly used medications with anti-inflammatory properties—like aspirin, angiotensin-converting enzyme inhibitors, methotrexate, and angiotensin receptor blockers[53]—have failed to consistently reduce biomarkers of immune activation and/or inflammation in people with HIV in randomized controlled trials and,[54-57] as a result, clinical outcome trials specific to this population are not anticipated.

Treatments Targeting Putative Drivers of the Inflammatory State

Other investigational approaches to reduce the inflammatory state in patients with viral suppression on ART have focused on the presumed root drivers of inflammation, including HIV reactivation from latently infected cells, microbial translocation, and chronic co-infections, particularly cytomegalovirus (CMV).[28] Thus far, the only approach targeting these root drivers that has broadly reduced systemic immune activation is treating asymptomatic CMV co-infection,[58] an approach that is being pursued further in a prospective larger trial (ACTG A5383). Presently, none of these strategies have been proven to be effective in clinical endpoint trials, so these interventions should be pursued only in the context of clinical trials.

Monitoring Inflammation

In the absence of proven interventions, there is no clear rationale to routinely monitor levels of immune activation and inflammation in treated HIV infection. Furthermore, many of the inflammatory markers that predict morbidity and mortality fluctuate significantly in individuals with HIV. Thus, clinical monitoring with immune activation or inflammatory markers **is not currently recommended (AII).** The focus of care to reduce chronic non-AIDS morbidity and mortality should be on maintaining ART-mediated viral suppression and addressing strategies to reduce risk factors (e.g., smoking cessation, healthy diet, and exercise) and managing chronic comorbidities, such as hypertension, hyperlipidemia, and diabetes **(AII).**

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Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

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Key Considerations and Recommendations
• Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance have made it possible to consider switching a person with HIV from an effective ARV regimen to an alternative ARV regimen in some situations. • The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options. • Adverse events, drug–drug or drug–food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt regimen optimization. • It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results before selecting a new ARV regimen (AI). • People with HIV who have no history of drug-resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ARV-naive patients (AI). • For regimen optimization in the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, two NRTIs—tenofovir alafenamide or tenofovir disoproxil fumarate plus emtricitabine (FTC) or lamivudine (3TC)—should be included in the regimen with a fully active, high resistance barrier drug, such as dolutegravir, boosted-darunavir (BIII), or bictegravir (CIII). • A long-acting ARV regimen of injectable cabotegravir (CAB) and rilpivirine (RPV) given every 1 or 2 months is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs (AI). • Pregnant persons who present to care on long-acting CAB and RPV should be switched to a *Preferred* or an *Alternative* three-drug ARV regimen recommended for use in pregnancy per the Perinatal Guidelines (AIII). • Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy is not recommended (AI). • When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued (AII) or specific anti-HBV drugs should be initiated. Using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended (AII), because HBV resistance to these drugs can emerge. Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage. • Consultation with an HIV specialist is recommended when planning a regimen switch for a patient with a history of resistance to one or more drug classes (AIII). • Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

With currently available antiretroviral therapy (ART), most people with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in antiretroviral (ARV) treatment and a better understanding of drug resistance have made it possible to consider switching a person with HIV from one effective regimen to another in some situations. When considering optimization—a

switch in therapy to improve some aspect of therapy—clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Adverse Effects of Antiretroviral Agents and Table 21 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug–drug interactions (see Drug–Drug Interactions)
- To eliminate food or fluid requirements
- To switch to a long-acting injectable regimen to relieve pill fatigue or to decrease potential stigma or disclosure concerns associated with taking daily oral medications
- To allow optimal use of ART during pregnancy or when pregnancy is desired or may occur (see Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Optimization

Maintain Viral Suppression

The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance mutations, the patient may require more complex and/or less tolerated regimens.

Careful Review of Antiretroviral Treatment and Drug Resistance History Before Optimization

The review of a patient's full ARV history, including virologic responses, cumulative resistance test results, and past ARV-associated intolerances, toxicities, and adverse reactions, is critical before any treatment switch **(AI).**

If a patient 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 patient was on the suppressive regimen. In patients with a history of virologic failure or pre-treatment drug resistance, a review of cumulative resistance test results and clinical and virologic response to prior regimens is essential when designing a new regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype (if available), phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a drug-resistance mutation—even when it is not detected in the patient's most recent drug-resistance test—can be archived in the HIV reservoir and reemerge under the appropriate selective drug pressure. Resistance often can be inferred from a patient's ARV history. For patients with documented failure on a regimen that includes drugs with relatively low barriers to resistance—such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC)—a clinician should assume that there is resistance to these drugs, so-called inferred resistance. When uncertain about prior resistance, it is generally not

advisable to switch from a suppressive ARV regimen, unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a relatively high barrier to resistance—such as those that include pharmacologically-boosted protease inhibitors (PIs), dolutegravir (DTG), or bictegravir (BIC)—to one with a lower barrier to resistance.[1] The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that clinicians consult an HIV specialist when contemplating optimization for a patient with a history of resistance to one or more drug classes **(AIII).**

If optimization is considered in patients with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For patients who have no prior virologic failures and who are on their first or second regimen, or for those who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide valuable information. In individuals with a history of multiple prior failures or multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. However, whenever proviral DNA genotypic testing is used, the results must be interpreted with caution because these assays may not detect all of a patient's drug-resistance mutations, especially those that were selected by a previous ARV regimen.[2] In addition, these assays may identify mutations that appear inconsistent with a patient's response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see Drug-Resistance Testing).

Optimization in a Person with Active Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with active hepatitis B virus (HBV)/HIV coinfection (HBsAg positive), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless another first-line HBV antiviral (e.g., entecavir) is initiated. Refer to the Hepatitis B Virus/HIV Coinfection section for specific recommendations. Both TDF and TAF are active against HBV and can be used as HBV monotherapy.[3] Discontinuation of HBV antivirals may lead to reactivation of HBV, which can result in serious hepatocellular damage. In people with HBV/HIV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII),** because HBV resistance to these drugs is likely to emerge. In patients with no documented history of or with no immunity to HBV infection, repeat HBV serology and re-vaccination should be completed if needed before optimization with a regimen that is not active against HBV.

Assessment for Potential Drug Interactions

Before switching a regimen, it is important to review each ARV drug in the new regimen and concomitant medications to assess whether any potential drug–drug interaction exists. For example, oral rilpivirine (RPV) and atazanavir interact with acid-lowering agents, and many ARV drugs may interact with rifamycin antibiotics (see Drug–Drug Interactions). In addition to new drug interactions, the discontinuation of some ARV drugs also may necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications, which may have been previously managed with dose adjustments, will need to be reevaluated in the context of the new ARV regimen.

Assessment for Pregnancy or Pregnancy Potential

People of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant or desires pregnancy, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use at the time of conception or during pregnancy. Recent controversies, based on observational data, about the use of integrase strand transfer inhibitors (INSTIs) pre-conception or during pregnancy are discussed further in the Perinatal Guidelines. All pregnancies that occur while an individual is receiving ART should be reported to the Antiretroviral Pregnancy Registry.

Monitoring After Switching Antiretroviral Therapy

After a treatment switch, patients should be evaluated closely for 3 months (e.g., a clinic visit or telephone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 8 weeks after the switch) **(AIII).** The purpose of this close monitoring is to assess medication tolerance and to conduct targeted laboratory testing if the patient has preexisting laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormality is a reason for the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

Specific Regimen Optimization Considerations

As with ART-naive patients, the use of a two- or three-drug combination regimen (as discussed below) is generally recommended when switching patients with suppressed viral loads **(AI).** Patients who have no history of resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ART-naive patients **(AI).** Patients with prior drug resistance can be switched to a new regimen based on their ARV history and cumulative resistance testing results. Monotherapy with either a boosted PI or an INSTI has been explored in several trials or cohort studies. Monotherapy has been associated with a higher rate of virologic failure than combination regimens and has been associated with the development of resistance, especially INSTI monotherapy; therefore, **monotherapy as an optimization strategy is *not recommended* (AI).**

Optimization Strategies with Good Supporting Evidence for People Without Known Drug Resistance

Many clinical trials have enrolled participants with stable, suppressed viral loads without known underlying drug resistance and switched them to another regimen. Most of these studies demonstrated maintenance of viral suppression; some of these studies are referenced below. However, some regimen switches have had limited success in clinical trials but have informed optimization strategies. The SWITCHMRK 1 and 2 studies illustrated the importance of considering the possibility of underlying drug resistance before switching therapy in those with virologic suppression.[1] This is particularly important when the new regimen may not include three fully active agents and when the new regimen may have a lower overall barrier to resistance. In the two SWITCHMRK studies, those with viral suppression on two nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies showed that individuals with a history of previous virologic failure had an increased risk of

virologic failure when switching to the RAL-based regimen. A possible explanation for this finding is that when only one of the accompanying NRTIs is fully active, viral suppression can be maintained by drugs with relatively high barriers to resistance, such as boosted PIs, DTG, and BIC, but not by those with lower barriers to resistance, such as EVG, RAL, and NNRTIs. The strategies listed below support these observations and principles of optimizing therapy.

Three-Drug Regimens

Within-Class Switches

Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, or lower pill burden or do not require PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. Examples of within-class switch strategies that have been studied in individuals without underlying drug resistance include the following:

- From TDF[4,5] or abacavir (ABC)[6] to TAF
- From RAL to DTG
- From DTG,[7-9] elvitegravir/cobicistat (EVG/c),[10] or RAL to BIC
- From efavirenz to RPV[5,11] or doravirine (DOR)[12]

Between-Class Switches

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. In general, such switches should be avoided if any doubt exists about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch. The following are between-class switches that have been studied:

- Replacing a boosted PI with an INSTI (e.g., DTG,[13] BIC[14] or EVG[15,16])
- Replacing a boosted PI with RPV[17] or DOR[12]
- Replacing an NNRTI with an INSTI[18,19]

Two-Drug Regimens

Growing evidence indicates that some two-drug regimens are effective in maintaining virologic control in patients who initiated therapy and achieved sustained virologic suppression for at least 3 to 6 months with three-drug regimens, provided their HIV is susceptible to both ARV drugs in the new regimen. However, because none of the two-drug regimens discussed below meet the standard of care for HBV treatment, these regimens are not recommended for individuals with HBV coinfection, unless the patient is also on a specific anti-HBV active regimen (e.g., entecavir) **(AIII).** Also see the section above on HBV considerations during optimization. The following are examples of successful strategies for switching from three- to two-drug regimens in people with suppressed HIV.

Dolutegravir plus Rilpivirine

Two Phase 3 trials, SWORD-1 and SWORD-2, demonstrated noninferior efficacy of DTG with RPV compared to continuing a first or second ARV regimen in individuals with suppressed HIV-RNA and without prior virologic failure, active Hepatitis B (unless the patient is also on a specific HBV active regimen), resistance to DTG or RPV, or significant drug interactions **(AI).**

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 patients with ongoing virologic suppression and no history of prior virologic failure or resistance to these agents was noninferior to continuing a three-drug therapy in a large randomized clinical trial (TANGO),[20] in smaller clinical trials,[21-23] and in observational studies[24-26] **(AI).** Individuals with active Hepatitis B infection need to be on a specific HBV active regimen, because 3TC or FTC monotherapy is not considered standard of care for HBV therapy.[3]

Boosted Protease Inhibitor plus Lamivudine

A boosted PI plus 3TC is a reasonable two-drug optimization option in individuals without resistance who are suppressed on a current regimen and who do not have active HBV infection. Pill burden and potential drug interactions are limitations compared to the above two-drug regimens. Several boosted PI plus 3TC regimens have been shown to be effective in clinical trials, including darunavir/ritonavir (DRV/r) **(BI)**[27] or darunavir/cobicistat (DRV/c) **(BIII),** atazanavir/ritonavir (ATV/r) **(CI),**[28,29] and LPV/r **(CI).**[30]

Boosted Darunavir plus Dolutegravir

An open-label, Phase 3b, noninferiority clinical trial evaluated continuation of DRV/r plus two NRTIs versus a switch to DRV/r plus DTG; the switched regimen was noninferior.[31] Because of the small sample size of this study, the regimen of DRV/r plus DTG is recommended only in the absence of other alternative options, but can be considered in particular for individuals with resistance and/or intolerance to 3TC (or FTC), ABC, and TDF (or TAF) **(CI).** Similar results were observed in two small observational studies.[32,33] This regimen is not suitable for individuals with active HBV infection, unless the patient is also on a specific HBV active regimen (e.g., entecavir).

Long-Acting Antiretroviral Therapy

Parenteral ARV medications with innate or enhanced long half-lives (by extended-release formulation) have been evaluated for use with less than daily dosing. Here, "long-acting" is defined as any medication that is dosed once weekly or less frequently. In 2018, in the United States, the first long-acting ARV medication—ibalizumab, an anti-CD4 monoclonal antibody, given intravenously every 2 weeks—was approved for use in combination with optimized background therapy in heavily treatment-experienced patients (see Virologic Failure). In January 2021, long-acting injectable formulations of the INSTI cabotegravir (CAB) and the NNRTI RPV were approved by the U.S. Food and Drug Administration (FDA). Multiple other long-acting ARV medications and/or drug delivery systems are being studied.[34]

Long-acting ARV medications provide the convenience of reduced dosing frequency and may improve quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or

stigma associated with daily oral medication. To date, ARV-experienced populations enrolled in completed clinical trials were selected based on their history of good adherence to their prescribed oral ART and were engaged in care as documented by a sustained undetectable viral load for at least 3 to 6 months at baseline. Thus, these therapies are recommended for similar populations that are consistently engaged in care. Concern exists that individuals who are less adherent to their medical care may miss doses or discontinue therapy, which can lead to an increased risk of virologic failure with resistance development. The long PK tail of long-acting ARVs can lead to prolonged periods of low drug levels or to differential exposure to just one drug in a regimen. The Panel awaits data from ongoing clinical trials in patients with suboptimal adherence and poor viremic control to assess the safety and efficacy of long-acting regimens in these patients.[35]

Cabotegravir plus Rilpivirine

Long-acting injectable CAB plus RPV is indicated in individuals with sustained (e.g., 3 to 6 months) virologic suppression (HIV-1 RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and with no known or suspected resistance to either CAB or RPV.[36] CAB is an INSTI and a structural analogue of DTG. RPV is an NNRTI first approved in an oral tablet formulation in 2011. A tablet formulation of CAB, available through the manufacturer but not in community pharmacies, was concurrently approved by the FDA to be used with RPV tablets as a 4-week oral lead-in therapy (dosing below, oral lead-in is not required) before initiation of the long-acting regimen and as oral bridging in the event of planned missed injections. This long-acting injectable combination can be given as once monthly or as an every 2-month therapy. Clinical trial data supporting these regimens are discussed below.

Clinical Trial Data

Two Phase 3 clinical trials (ATLAS and FLAIR), which enrolled almost 1,200 participants with HIV-1, evaluated once-monthly intramuscular (IM) injections of CAB combined with RPV.[37,38] Participants could not have prior resistance to INSTIs or NNRTIs (except the K103N mutation), previous virologic failure (ATLAS trial), or HBV infection that was active or occult. In ATLAS, participants were virally suppressed for at least 6 months on standard oral ART prior to randomization. In FLAIR, ARV-naive participants who achieved HIV viral suppression by 16 to 20 weeks on oral DTG/ABC/3TC were then randomized to long-acting injectable CAB and RPV once monthly versus continued oral therapy. Both studies used a 1-month oral lead-in of once-daily CAB 30 mg with RPV 25 mg taken with food. On the day of the last oral doses, injectable CAB 600 mg (3 mL) with injectable RPV 900 mg (3 mL) were administered via separate ventrogluteal IM injections. After the loading dose, separate ventrogluteal IM injections of CAB 400 mg (2 mL) with RPV 600 mg (2 mL) were administered monthly.

In the intention to treat exposed population, HIV RNA >50 copies/mL at Week 48 occurred in 11 participants (1.9%) in the IM long-acting arm and 10 participants (1.7%) in the oral therapy arm (combining data from both studies).[39] This demonstrated noninferiority of long-acting injectable CAB and RPV compared with continuing the oral three-drug standard of care. Virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common. Week 96 results confirmed noninferiority of every 4-week long-acting injectable CAB and RPV compared with oral regimens.[40]

ATLAS-2M was an open-label, Phase 3b, noninferiority study of long-acting injectable CAB plus RPV administered IM every 8 weeks (CAB 600 mg plus RPV 900 mg) (n = 522) versus every

4 weeks (CAB 400 mg plus RPV 600 mg) (n = 523) to treatment-experienced adults with HIV-1. Thirty-seven percent of patients were rolled over from the ATLAS trial.[41] Other enrollees had undetectable HIV viral load for at least 6 months on a stable, oral ARV regimen. Every 8-week dosing in individuals naive to long-acting therapy consisted of a month-long oral lead-in (same as in the ATLAS and FLAIR trials above), followed by injections beginning on the last day of oral therapy, repeated 4 weeks later, then given every 8 weeks. All doses were CAB 600 mg (3 mL) plus RPV 900 mg (3 mL) administered IM in separate ventrogluteal sites. At 48 weeks, long-acting CAB plus RPV administered every 8 weeks was noninferior to the every 4-week dosing (HIV RNA ≥50 copies/mL; 2% vs. 1%).[40] These results were confirmed at 96 weeks. Safety was similar between the long-acting CAB plus RPV 8-week versus 4-week administration groups.[42] Resistance analyses are discussed below. The results of this study led to the approval of every 2-month IM dosing for long-acting injectable CAB 600 mg (3 mL) plus RPV 900 mg (3 mL) by the FDA in January 2022.

Adverse Events When Using Long-Acting Cabotegravir and Rilpivirine

Adverse events were more common in individuals receiving IM long-acting CAB and RPV in both the ATLAS and FLAIR trials compared to those continuing oral therapy. Injection site reactions (ISRs) were the most common adverse events and occurred in more than 80% of participants, at least once. ISRs were less common over time, occurring in about 10% to 30% of participants at each monthly IM injection timepoint after the first year. ISRs were generally mild to moderate, with 99% being Grade 1 or 2 and the median duration of symptoms being 3 days. Four percent of patients experienced at least one Grade 3 ISR; 1% discontinued long-acting injectable treatment because of an ISR. Hypersensitivity reactions, post-injection reactions, hepatotoxicity, and depressive disorders also have been reported.[40,43]

Panel's Recommendation

Data from the ATLAS, FLAIR, and ATLAS-2M trials support that separate monthly or every 2-month ventrogluteal IM injections of CAB and RPV can be used to replace an existing oral ARV regimen in people with HIV with sustained viral suppression for 3 to 6 months (optimal duration is not defined) **(AI).** Criteria for use should include individuals who have good adherence and engagement in care, with no baseline resistance to either medication, no prior virologic failures; who do not have active or occult HBV infection (unless the patient also is receiving an HBV active regimen [e.g., entecavir]); who are not pregnant or planning on becoming pregnant; and who are not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV. Oral lead-in therapy with CAB and RPV is optional and can be done based on provider–patient discussion. In the FLAIR Extension study, after 100 weeks in the oral standard of care ART arm, 232 participants switched to long-acting CAB with RPV with or without an oral lead-in per patient preference.[43] After 24 weeks, there were no differences in adverse events, tolerability, efficacy, or PKs between the direct-to-inject and oral lead-in extension arms.

Practical Considerations When Using Long-Acting Injectable Cabotegravir and Rilpivirine

Practical considerations regarding the feasibility of monthly or every 2-month IM administration of CAB and RPV deserve attention. Because the currently approved formulations are recommended to be administered only by a health care provider, the potential exists for strain on clinical systems, pharmacies, and patients. A 23-gauge, 1½-inch IM needle is recommended for the injection and is provided in the product packaging. However, longer, 2-inch needles should be used in patients with body mass index >30 kg/m^2. Ventrogluteal IM injections should be given on opposite sides when

possible, or at least 2 cm apart if given on the same side. Individuals with buttock implants or fillers may not be appropriate candidates because of concerns regarding drug absorption. Care should be taken to administer only into gluteal muscle, preferably ventrogluteal. Several drugs, particularly those interacting with cytochrome P450 3A or uridine diphosphate glucuronosyltransferase 1A1, are contraindicated with CAB and RPV (oral and/or IM) due to significant drug interactions, including certain anticonvulsants and rifamycins. For other specific storage, preparation, and administration details, please review the Drug-Drug Interaction Tables 24b and 24d.

Management of Missed Doses of Long-Acting Injectable Cabotegravir and Rilpivirine

Long-acting CAB and RPV have extended half-lives (6 to 12 weeks for CAB and 13 to 28 weeks for RPV), and detectable concentrations may be present for ≥12 months after the last dose.[36] Individuals who miss doses or discontinue therapy without starting an oral regimen are at increased risk of virologic failure with development of drug resistance. Population PK modeling of delayed injections in the bimonthly dosing suggests that delays of over 1 week will lead to significantly reduced drug exposure. Patients should be fully informed of this risk. The prescribing information for IM CAB and RPV should be consulted for guidance on managing missed doses. Recommendations differ based on the dosing being utilized (monthly vs. every 2 months), as well as the timing of the missed dose. Oral-bridging therapy should be made available for planned missed doses. Unplanned missed doses (beyond the 7-day window) should prompt reevaluation of whether the person remains an appropriate candidate for injectable therapy. When stopping therapy, transition to a suppressive oral regimen should occur within 4 weeks of the last IM doses on monthly dosing and 8 weeks of the last IM doses for every 2-month dosing.

HIV Viral Load and Drug-Resistance Testing Monitoring

HIV viral load monitoring should be performed 4 to 8 weeks after a switch to long-acting CAB and RPV. HIV viral load also should be checked in patients with unplanned missed visits and delayed dosing of long-acting CAB and RPV. When viremia develops during long-acting therapy, resistance testing, including integrase resistance testing, should be performed. Follow-up dosing in patients with missed IM doses should not be delayed while waiting for viral load and resistance test results. In a pooled analysis from the FLAIR, ATLAS, and ATLAS-2M trials, confirmed virologic failure was more common in the setting of baseline, proviral, RPV resistance-associated mutations; HIV-1 subtype A6/A1 (rare in the United States); higher baseline body mass index; and lower Week-8 trough RPV concentration.[44]

In ATLAS-2M, in the every 8-week arm, of 11 participants with confirmed virologic failure at 152 weeks, six had baseline proviral DNA-resistance mutations to NNRTIs and one to INSTIs. The study suggested that baseline, proviral, RPV resistance-associated mutations had a greater impact on virologic failure and resistance in the every 8-week arm compared with the every 4-week arm. At virologic failure, 9 of 11 participants in the every 8-week arm had NNRTI resistance, and 7 of these 9 participants also had INSTI resistance. Two participants in the every 4-week arm had virologic failure, neither had baseline proviral DNA resistance; although both had dual-class resistance to NNRTIs and INSTIs at virologic failure.[45] In patients who develop resistance to CAB or RPV or both drugs, the regimen should be changed based on resistance test results (see Virologic Failure). Consultation with an expert in HIV drug resistance should be considered.

Pregnancy Considerations

Oral CAB and the long-acting injectable regimen of CAB and RPV have been classified as **not recommended** for use in pregnancy, because insufficient data exist for people who are trying to conceive or who become pregnant while on this regimen. Management of patients who become pregnant while on therapy will need close oversight. Because data about the use of CAB and RPV during pregnancy are extremely limited, the Panel recommends that pregnant individuals who present to care on this regimen should be switched to a *Preferred* or *Alternative* three-drug ARV regimen recommended for use in pregnancy per the Perinatal Guidelines **(AIII).** In clinical trials to date, most participants who became pregnant were switched from IM CAB and RPV to an alternative ARV regimen for the remainder of their pregnancies.[46,47] In 11 live births from individuals with HIV who conceived after receipt of CAB and RPV (1 oral, 10 IM dosing), one congenital anomaly of congenital ptosis in a preterm infant with intrauterine growth restriction occurred.[47] To date, in the small number of individuals who became pregnant during long-acting CAB and RPV dosing, plasma CAB and RPV concentrations have been in the range expected for non-pregnant people. Health care providers are strongly encouraged to register people who become pregnant while receiving IM CAB and RPV with the Antiretroviral Pregnancy Registry.

Other Considerations

CAB and RPV do not have HBV activity. Patients with active or occult HBV were excluded from all clinical trials of long-acting CAB and RPV to date. If CAB with RPV is used in patients with active or occult HBV, additional, specific treatment for HBV infection is needed (see Hepatitis B Virus/HIV Coinfection).

Many patients with HIV are on oral therapy for medical, preventive, or mental health comorbidities. Counseling will be needed to emphasize the importance of continued adherence to oral therapies for other indications.

Optimization Strategies for People with Viral Suppression and a History of Limited Drug Resistance

Some existing data demonstrate the safety and efficacy of within-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). However, data are limited regarding between-class switches in this population, and support for such a switch generally depends on findings extrapolated from non-optimization studies, as discussed below.

*Within-Class Switch from Dolutegravir to Bictegravir **(BI)***

The GS 4030 study enrolled 565 individuals 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. This is a switch from a high-barrier drug, DTG, to another high-barrier drug, BIC. After 48 weeks, the groups had similar rates of sustained suppression. The rates of viral suppression were similar for those with a documented history of NRTI resistance (approximately 25% of participants) and those without a history of NRTI resistance.[48] Results from this trial lend theoretical support to other optimization strategies that include a switch from one high-barrier drug to another in the setting of a similar NRTI backbone. This study also supports the recommendation that when

using drugs with a high barrier to resistance, only one of the NRTIs needs to be active. This is supported by other lines of evidence, some of which are discussed below.

Other Switches to Bictegravir in the Setting of Limited Drug Resistance

The BRAAVE study was an open-label, optimization study for Black people with HIV and viral suppression for ≥12 months on a standard regimen of two NRTIs plus a third agent (INSTI, NNRTI, or PI). Individuals were randomized to switch to BIC/FTC/TAF or to remain on current therapy (although individuals on TDF were switched to TAF). Switching to BIC-based therapy was noninferior for maintaining viral suppression compared with continuing current oral therapy. Baseline regimens included 61% INSTI, 31% NNRTI, and 9% PI. Baseline resistance did not affect the outcomes of therapy. In particular, NRTI resistance was present in 14% of participants, and 10% harbored the M184V/I mutation.[49]

Data from Non-Optimization Studies Inform Optimization in Clinical Practice

Several studies of ART changes in the setting of first-line NNRTI-based virologic failure support the use of specific treatment combinations for optimization, as well as the fact that drugs with a high barrier to resistance need only one, or possibly no, fully active NRTIs paired with them. In the DAWNING study,[50] in individuals failing first-line NNRTI-based therapy, individuals with one active NRTI in their next regimen had similar virologic responses as those with two active NRTIs. Overall, viral suppression to <50 copies/mL at Week 48 was more common with DTG (84%) than LPV/r (73%). In the NADIA study, 464 participants with virologic failure on initial NNRTI-based therapy (NNRTI plus TDF and either 3TC or FTC) were randomized to either DTG or DRV/r, and within each arm randomized to either TDF/3TC or zidovudine (ZDV)/3TC. At enrollment, resistance to NRTIs was common with 86% of individuals having an M184V mutation and 50% having a K65R mutation. Dual-NRTI resistance was present in 172 (37%) individuals. At 48 weeks, DTG was noninferior to DRV/r with both achieving viral suppression to <400 copies/mL in about 90% of individuals. There were no differences in rates of viral suppression between individuals with resistance to one or both NRTIs in their regimens. At 96 weeks of follow-up, TDF was superior to ZDV, with 92% of those on TDF-based therapy and 85% of those on ZDV-based therapy achieving viral suppression to <400 copies/mL.[51]

In both the DAWNING and NADIA trials described above, the presence of baseline NRTI resistance to one or both NRTIs used in the new regimen did not lower rates of viral suppression compared with individuals without NRTI resistance. Although these were studies of ART use in the setting of initial NNRTI-based virologic failure and not optimization in patients with viral suppression, regimens that are effective during viremia should be at least as effective in the setting of viral suppression in individuals 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 existing NRTI resistance, two NRTIs (TAF or TDF plus 3TC or FTC) should be included in the regimen with a fully active, high resistance barrier drug, such as DTG **(BIII),** a boosted DRV **(BIII),** or BIC **(CIII).** The use of no fully active NRTIs **is not routinely recommended** when there are other viable treatment options. However, in some clinical situations—such as when prior resistance testing is not fully available, to avoid major drug–drug interactions, to keep regimens simpler, or for other reasons—a regimen with a fully active, high resistance barrier drug combined with two partially active NRTIs can be considered. Both tenofovir and cytidine analogs may retain partial activity even when resistance is present. Future clinical trials of such regimens are necessary before this practice can be routinely recommended.

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

Before optimization of the ARV regimen of a person with viral suppression who has a history of treatment failure and drug resistance, a careful review of the individual's ARV history and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII).**

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir

Switching to the combination of EVG/c/TAF/FTC plus DRV has been shown to be a potential optimization strategy in patients on complicated salvage regimens.[52] A randomized controlled trial enrolled 135 patients with virologic suppression who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Participants had up to three thymidine analog resistance mutations and/or the K65R mutation but no history of either the Q151M mutation or T69 insertion. The participants were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their current regimen. At 48 weeks, optimization to EVG/c/TAF/FTC plus DRV was superior to continuation on a current regimen, with 94.4% of participants in the switch arm and 76.1% in the continuation arm maintaining viral suppression. With regimen simplification, the pill burden was reduced from an average of five tablets per day to two tablets per day.[52] EVG/c/TAF/FTC plus DRV would be an appropriate option for individuals who have treatment and drug resistance histories similar to those of participants included in this study **(AI).**

Optimization Strategies Not Recommended

Boosted Protease Inhibitor Monotherapy

The strategy of switching patients with virologic suppression without PI resistance from one ARV regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and to decrease costs while taking advantage of the high barrier to resistance of PIs. PI/r monotherapy maintains virologic suppression in most patients but at lower rates than regimens that include one or two NRTIs.[53-55] Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy than with regimens that include one or two NRTIs. In most studies, resuming NRTIs in patients who are experiencing low-level viral rebound has led to re-suppression.[56-59] Clinical trials have not evaluated the use of coformulated cobicistat-boosted PI regimens as monotherapy or compared different PI/r monotherapy regimens. Based on the results from these studies, boosted-PI monotherapy **is not recommended (AI).**

Dolutegravir Monotherapy

The strategy of switching patients with virologic suppression to DTG monotherapy has been evaluated in cohort studies, in clinical practice,[60,61] and in a randomized controlled trial.[62] This strategy has been associated with an unacceptable rate of virologic failure and subsequent development of INSTI resistance; therefore, a switch to DTG monotherapy **is not recommended (AI).**

Boosted Atazanavir plus Raltegravir

In a randomized study, patients with virologic suppression switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. The ATV/r plus RAL regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the switch to ATV/r plus TDF/FTC.[63] A regimen consisting of ATV/r plus RAL **cannot currently be recommended (AI).**

Maraviroc plus Boosted Protease Inhibitor

In a randomized controlled trial, patients with virologic suppression who were on a regimen of two NRTIs plus a boosted PI and who had only CCR5-tropic HIV (as detected by proviral DNA testing) were randomized to continue their current regimen or to switch to maraviroc (MVC) plus two NRTIs or to MVC plus a boosted PI. The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC **cannot be recommended (AI).**[64]

Maraviroc plus Raltegravir

In a nonrandomized pilot study, patients with virologic suppression were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in 5 out of 44 patients.[65] Based on these study results, use of MVC plus RAL **is not recommended (AII).**

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Discontinuation or Interruption of Antiretroviral Therapy

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Discontinuation or interruption of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and/or clinical progression.[1-5] Thus, discontinuation or planned interruption of ART is not recommended outside the context of a clinical trial **(AI).** However, unplanned interruption of ART may occur under certain circumstances as discussed below.

Unanticipated Interruptions of Oral Antiretroviral Drugs

Reasons for short-term interruption (days to weeks) of ART vary and may include intercurrent illnesses that preclude oral intake (e.g., gastroenteritis, pancreatitis), surgical procedures, drug toxicity, or interrupted access to antiretroviral (ARV) drugs. Stopping ART for a short time (i.e., less than 1 day to 2 days) usually can be done by holding all drugs in the regimen. Whether unplanned interruptions occur by accident or by necessity (e.g., because of drug toxicities), all efforts should be made to minimize their duration. Recommendations for some specific scenarios are listed below.

When a Patient Experiences Unexpected Inability to Take Solid Oral Medications

For patients who require tube feeding, some ARV drugs are available in liquid formulations, and some pills may be crushed. The Oral Antiretroviral/HCV DAA Administration[6] provides information on crushing pills and formulating liquid ARV drugs. Additional information also may be available in drug product labels. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way for a patient with a feeding tube to continue an effective ARV regimen.

For patients unable to take medications by any enteral route (e.g., in the context of severe gastrointestinal disease), all components of the oral drug regimen should be stopped simultaneously, regardless of half-lives of the drugs. After resolution, all components of the ARV regimen should be restarted simultaneously.

Several ARV drugs are available as parenteral formulations; these include zidovudine, enfuvirtide, ibalizumab (IBA), and the long-acting (LA) injectable formulations of cabotegravir (CAB LA) and rilpivirine (RPV LA). The combination of CAB LA and RPV LA is approved as a complete regimen for the treatment of HIV. However, this regimen has not been studied as an alternative for patients who cannot take oral medications. Clinicians should consult with an HIV specialist before prescribing any of these agents.

When a Patient Experiences a Severe or Life-Threatening Toxicity to an Antiretroviral Agent

All components of the ARV drug regimen should be stopped simultaneously, regardless of drug half-life. After resolution, a different complete regimen that does not include the offending agent should be started.

Interruption of Long-Acting Antiretroviral Drugs

The combination of CAB LA and RPV LA is approved as a complete regimen for the treatment of HIV. CAB LA and RPV LA are given as intramuscular (IM) injections and have extended half-lives. Therefore, patients who miss doses or discontinue therapy without bridging with an oral ARV regimen are at increased risk of virologic failure with development of drug resistance. Clinicians should refer to prescribing information for CAB LA and RPV LA for the management of missed doses or discontinuations.[7] For planned missed injection doses of CAB LA and RPV LA, oral formulations of CAB and RPV should be made available to patients as a bridging therapy for up to 2 months. Oral formulation of RPV is available by prescription in community pharmacies, but oral formulation of CAB is available only through the manufacturer. When stopping long-acting injectable ART, transition to a suppressive oral ARV regimen should occur within 4 weeks of the last planned IM doses. Patients who have missed or delayed clinic visits repeatedly should be reassessed to determine if resumption of injections is appropriate or if they may need to be transitioned back to an oral regimen. Plasma viral load testing should be performed before the transition, and drug-resistance testing should be considered if plasma viremia is present.

Patients with drug-resistant HIV may receive IBA as part of a salvage regimen. IBA is initiated with a 2,000-mg loading dose given as an intravenous (IV) infusion, then followed by 800 mg given as an IV infusion every 14 days as maintenance therapy. If a dose is missed by ≥3 days, a repeat loading dose of 2,000 mg IV infusion is recommended before resumption of maintenance therapy.

Analytical Treatment Interruption

Several research studies are evaluating approaches to achieve sustained ART-free viral remission or a functional cure for HIV.[8] Viral eradication (i.e., elimination of HIV entirely from an individual) remains a more challenging, longer-term goal. Currently, the only way to reliably test the effectiveness of these strategies is to interrupt ART and closely monitor for viral rebound in the setting of a clinical trial, an approach referred to as "analytical treatment interruption" or ATI.[9] The duration of treatment interruption, the dynamics of viral rebound, and the criteria for restarting ART are part of ATI clinical trial designs with the goal to conduct these clinical trials safely.

Before ART is interrupted, participants of ATI trials should be made aware of and understand the risks of viral rebound,[10] acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations (e.g., oral thrush) or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), and the development of drug resistance. Patients should be counseled about the need for close clinical and laboratory monitoring during ART interruptions and provided counseling and linkage to pre-exposure prophylaxis services should they wish to refer sexual partners at risk for acquiring HIV.

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Considerations for Antiretroviral Use in Special Patient Populations

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) and to prevent transmission of HIV (AI). Monitoring of plasma HIV RNA levels, CD4+ T lymphocyte 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 the initiation of ART (AIII). • ART can be initiated before drug-resistance test results are available. For those without a history of prior use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), one of the following ARV regimens is recommended (AIII): o Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC) o Dolutegravir (DTG) with (TAF or tenofovir disoproxil fumarate [TDF])[b] plus (FTC or lamivudine [3TC]) o Boosted darunavir (DRV) with (TAF or TDF)[b] plus (FTC or 3TC) • For those with a history of CAB-LA use as PrEP, genotype testing done before the start of ART should include screening for integrase strand transfer inhibitor (INSTI)-resistance mutations: o A regimen of boosted DRV with (TAF or TDF)[b] plus (FTC or 3TC) is recommended—pending the results of the genotype testing (AIII). o Use of 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 become infected during and possibly after the use of CAB-LA as PrEP. • Pregnancy testing should be performed in persons of childbearing potential before initiation of 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 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.

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 HIV RNA test or p24 antigen test. Recent HIV infection is considered the phase 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 can be relatively mild or the person can be asymptomatic.[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 12 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 high-risk behavior (see Table 12 below).[7] Individuals may not always disclose high-risk behaviors or perceive that such behaviors put them at risk for HIV acquisition. Thus, even in the absence of reported high-risk behaviors, 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 recommends routine screening for HIV infection 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%) patients presenting with flu-like symptoms.[8] Acute HIV infection also was diagnosed in 7 of 563 (1.2%) patients 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 following websites: AIDSVu and the Centers for Disease Control and Prevention (CDC)'s AtlasPlus.

Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV p24 antigen (Ag/Ab assays) are part of the recommended initial laboratory HIV testing algorithm,[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 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] Patients 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 receiving 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, it 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 patient with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV RNA test result (>200 copies/mL)[18] indicate that acute HIV infection is highly likely.

Diagnosing Acute HIV Infection in People Taking Pre-Exposure Prophylaxis

Three antiretroviral (ARV) options, oral emtricitabine (FTC) with either tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), and intramuscular long-acting cabotegravir (CAB-LA) are now available for HIV pre-exposure prophylaxis (PrEP). People who acquire HIV while taking PrEP may sometimes have ambiguous HIV test results. A positive HIV Ag/Ab test result or a positive HIV RNA test result in the setting of a negative HIV antibody test result should prompt immediate confirmation of HIV diagnosis. It is important to collect a new blood specimen to verify the HIV diagnosis before initiating ART. Important considerations include the following:

- In people with HIV RNA level ≥200 copies/mL who are taking PrEP, immediate initiation of an effective HIV treatment regimen[19,20] is recommended while awaiting confirmation of HIV diagnosis **(AIII).**
- In people taking PrEP who have a negative HIV antibody test result and a very 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.[21] Options for confirming HIV infection and managing such cases is an area of evolving science recently summarized by the CDC.[21] Clinicians seeking urgent advice can contact the Clinical Consultation Center's PrEP Service at 1-855-HIV-PREP.

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 into each arm, 25 incident cases of HIV were identified in the CAB-LA arm.[22,23] Selection of a potent ARV regimen in persons who develop acute HIV infection while taking CAB-LA for PrEP should consider that injectable CAB may remain detectable after treatment discontinuation, for up to 3 years in men and 4 years in women.[24] This long pharmacokinetic tail may contribute to the selection of drug-resistant variants in the setting of incident infection. When diagnosing acute HIV infection in people taking CAB-LA or in people with a history of prior CAB-LA PrEP use, treatment with a non-integrase strand transfer inhibitor (INSTI)-based regimen (see Antiretroviral Regimens for Early HIV Infection below) is recommended **(AIII)** while awaiting confirmation of HIV drug resistance-test results.

Treating Early HIV Infection

The goals of ART during early HIV infection are to suppress plasma HIV RNA to undetectable levels **(AI),** to prevent the transmission of HIV **(AI),** and to 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. 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.[30-42] In addition, early HIV infection is considered a period of high infectivity,[43] and early ART has been shown to substantially reduce the risk of HIV transmission.[44-47]

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 transmitted virus that were resistant to at least one ARV drug in up to 16% of people with HIV.[48,49] In one study, 21% of isolates from persons with acute HIV infection demonstrated resistance to at least one ARV drug, most commonly non-nucleoside reverse transcriptase inhibitors (NNRTIs).[50-52] Therefore, before initiating ART in a person with early HIV infection or low qualitative or quantitative plasma HIV RNA test result (<200 copies/mL), a blood specimen should be sent for drug-resistance testing, although treatment should not be delayed pending resistance-test results. The test results should be used to modify the ARV regimen if necessary **(AII).** The Panel on Antiretroviral Guidelines for Adults and Adolescents does not currently recommend routine genotype testing for INSTI resistance in treatment-naive persons given the low rate of transmitted INSTI resistance and the high barrier to resistance of dolutegravir (DTG) and bictegravir (BIC), unless

transmitted INSTI resistance is a concern **(AIII).** However, the rate of transmitted INSTI resistance has increased (from 0.8% to 1.1%, $P = 0.04$) with the increasing use of INSTIs, indicating a need for ongoing population monitoring.[53,54] Genotype testing for INSTI resistance should be performed for those who become infected during or after the use of CAB-LA as PrEP **(AIII).**[24]

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 **(AII).** 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 persons of childbearing potential should have a pregnancy test before initiating ART **(AIII).**

If ART is to be initiated before the results of drug-resistance tests are available, one of the following regimens is an appropriate option for individuals who have not received CAB-LA prior to diagnosis of acute HIV **(AIII):**

- DTG with (TDF or TAF plus lamivudine [3TC] or FTC)
- BIC/TAF/FTC
- Boosted darunavir (DRV) with (FTC or 3TC) plus (TAF or TDF)

DTG, BIC, and boosted DRV are all good treatment options, because transmitted resistance to each of these agents is rare, and they all have a high barrier to resistance.

For individuals with acute HIV who become infected during and after the use of CAB-LA as PrEP, use of an INSTI-based regimen **is not recommended (AIII).** The recommended regimen, at least until resistance testing confirms the absence of INSTI-resistance mutations, is a boosted DRV with (FTC or 3TC) plus (TAF or TDF) **(AIII).**

Preliminary data from a birth outcomes surveillance study in Botswana suggested an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[55] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[56] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should perform a pregnancy test. Clinicians should discuss the risks

and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision.

A pharmacologically boosted protease inhibitor (PI)-based regimen (e.g., boosted DRV) is also an option because resistance to PIs emerges slowly, and clinically significant transmitted resistance to PIs is uncommon. Abacavir/3TC **is not recommended** for treatment of acute HIV infection, unless the patient is known to be HLA-B*5701 negative—information that is seldom available when individuals with acute infection are diagnosed. Therefore, TDF/FTC or TAF/FTC 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 Patients 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 as PrEP,[57-59] early HIV infection may be diagnosed in some persons while they are taking TDF/FTC. In this setting, drug-resistance test results are particularly important; however, the regimens listed above remain as reasonable treatment options pending drug-resistance test results.

Because the rate of transmitted drug resistance for NNRTIs is relatively high, 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 persons of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII).** Because early HIV infection, especially in the setting of high-level viremia, is associated with a high risk of perinatal transmission, all pregnant people with HIV should start combination ART as soon as possible to prevent perinatal transmission. Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Follow-Up After Antiretroviral Therapy Initiation

After ART initiation, monitoring of plasma HIV RNA levels, CD4+ T lymphocyte counts, and adverse effects should be performed as described in Laboratory Testing for Initial Assessment and Monitoring of Patients 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, thereafter, every 3–4 months) **(AII).**

Table 12. 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 individuals with the signs, symptoms, or laboratory findings described below and in asymptomatic individuals with a possible recent (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 a person who has HIV or a person at risk of HIV infection; sharing needles and syringes to inject drugs, as well as equipment used to prepare drugs for injection; or any exposure in which an individual's mucous membranes or any breaks in the skin come in contact with bodily fluid that potentially carries 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/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.

ART 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 and to prevent HIV transmission (AII).
- All persons of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test (AIII).
- Pregnant people with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV (AI).
- A blood sample for genotypic drug-resistance testing should be obtained before initiation of ART to guide the selection of the regimen (AII), but ART should be initiated as soon as possible, often before resistance-test results are available. If resistance is subsequently identified, treatment should be modified as needed.

Table 12. Identifying, Diagnosing, and Treating Acute and Recent HIV Infection

- ART can be initiated before the results of drug-resistance testing are known. For individuals who do not have a history of prior use of CAB-LA as PrEP, one of the following ARV regimens is recommended (AIII):
  - DTG with (TAF or TDF)[b] plus (FTC or 3TC)
  - BIC/TAF/FTC
  - Boosted DRV with (TAF or TDF)[b] plus (FTC or 3TC)
- For individuals with a history of prior use of CAB-LA as PrEP, genotypic resistance testing done before the start of ART should include screening for INSTI-resistance mutations. Recommended regimens include the following:
  - Boosted DRV 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 become infected during the use of CAB-LA and possibly up to 4 years after.
- Pregnancy testing should be performed in persons of childbearing potential before initiation of ART (AIII).
- Preliminary data from a birth outcomes surveillance study in Botswana suggested an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.[56] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[56] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should discuss the risks and benefits of using DTG to allow them to make an informed decision.

[a] In some settings, behaviors that increase the risk of HIV infection may not be recognized or perceived as risky by the health care provider, the patient, or both. Thus, even in the absence of reported high-risk behaviors, 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.

Key: 3TC = lamivudine; Ag/Ab = antigen/antibody; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CAB-LA = cabotegravir long-acting; CMV = cytomegalovirus; DRV = darunavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Adolescents and Young Adults with HIV

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Key Considerations and Recommendations
• Adolescents and young adults (AYA) with HIV largely belong to two distinct groups: those who acquired HIV in the first decade of life and who may be heavily antiretroviral therapy (ART)–experienced (early-acquired HIV); and those who acquired HIV in or after the second decade of life who may be mostly ART-naive. • ART is recommended for all AYA with HIV (AI) to reduce HIV-related morbidity, mortality, and transmission. • For AYA with HIV who are at risk for poor clinical outcomes, it is critically important to assess the behavioral and psychosocial context, and their ability to adhere to ART. Efforts should be made to provide youth-friendly support and infrastructure to reduce barriers to adherence and maximize success in achieving sustained viral suppression (AIII). • Pediatric and adolescent care providers should prepare AYA with HIV for the transition into adult care settings. Adult providers should be knowledgeable about this unique patient population and the challenges that frequently accompany the transition into the adult care setting. Consulting and collaborating with pediatric and adolescent HIV care providers is critical to ensure the successful transition of AYA with HIV to adult providers and continued engagement in care (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Adolescents (13–19 years old) and young adults (20–24 years old) (AYA) with HIV consistently account for about one-fifth of new infections in the United States.[1] AYA with HIV have lower rates of testing, diagnosis, treatment engagement, and viral suppression than adults with HIV. Importantly, unique developmental, psychosocial, behavioral, and infrastructural factors affect this vulnerable population. Without having their specific challenges and needs addressed, AYA with HIV remain at risk for poorer HIV-related outcomes, including persistent viremia, drug resistance, morbidity, mortality, and secondary transmission.

Epidemiology

Globally, approximately 5 million young people aged 15 to 25 years live with HIV.[2] AYA with HIV are mostly individuals who acquired HIV in the first decade of life, mainly perinatally and rarely via blood transfusion or from sexual abuse. During adolescence and young adulthood, most individuals acquire HIV through sexual activity. Among the latter group, the Centers for Disease Control and Prevention (CDC) estimates that consistently one-fifth of the approximately 40,000 individuals newly diagnosed with HIV in the United States annually are adolescents and young adults.[1] The majority of new infections in this age group are among Black/African Americans and Hispanic/Latino males who identify as men who have sex with men (MSM). For example, in 2018, more than 50% of the infections in this age group were among young Blacks and African Americans, and 27% were among Hispanics and Latinos. Most (87%) were male, with 92% identifying as MSM. Compared to adults with HIV, AYA with HIV are less likely to have acquired HIV from injection drug use, and trends in HIV and AIDS prevalence indicate that the disproportionate burden of HIV among racial and ethnic minorities is even greater among youths 13 to 24 years of age than among

those older than 24. Together, AYAWH account for approximately 34,000 of the individuals being followed at pediatric and adult clinics in the United States.[3]

Heterogeneity of Adolescents and Young Adults with HIV

AYA with HIV represent a diverse population in terms of socio-demographics, mode of HIV acquisition, sexual and substance use history, clinical and immunologic status, psychosocial development, and ability to adhere to medications. These distinctions have implications for HIV treatment, including the best ways to support AYA with HIV to optimize outcomes. AYA with HIV largely belong to two distinct groups:

- ***Adolescents and Young Adults with Early-Acquired HIV:*** These individuals, who acquired HIV in the first decade of life, are more likely to be treatment-experienced and have antiretroviral (ARV) drug resistance that may limit their options for ART regimens. This may be even more relevant for AYA with HIV who emigrated from parts of the world where routine viral load and genotypic resistance testing are not as readily available so that recognition of virologic failure and drug resistance may be delayed or missed. Also, individuals in this group generally have undergone a longer duration of disease chronicity and may have greater disease burden and more complications, less functional autonomy, and higher mortality risks.[4]
- ***Adolescents and Young Adults with HIV Acquired Later in Life:*** Individuals in this group are a more heterogeneous group of mostly young men (especially MSM) and young cisgender and transgender women with HIV acquired primarily through sexual activities. A minority in this group have acquired HIV through injecting drugs or were victims of sexual abuse. The intersection of adolescence and young adulthood with other key risk populations (e.g., MSM, people who use drugs, transgender individuals) magnifies the risk of poor clinical outcomes in this younger population. A statistically higher percentage of individuals in this group reported experiencing an even more extensive number of negative life experiences compared to those who acquired HIV early in life (38.8% versus 16.3%, $P<.012$).[5]

Unique Characteristics and Considerations for Adolescents and Young Adults with HIV

Although a diverse group, many AYA with HIV share unique characteristics that distinguish them from adults with HIV. Furthermore, AYA with HIV have certain commonalities that, while not necessarily unique to youth, disproportionately affect their chances of successful HIV treatment. Compared to adults 25 years old and older, AYA with HIV have poorer outcomes on each step of the HIV care continuum[6] (i.e., HIV diagnosis, linkage to HIV care, receipt of care, retention in care, achievement of viral suppression, maintenance of viral suppression). Most notably, only 40% of AYA with HIV are aware of their diagnosis and only 6% to 30% are virally suppressed.[7] These numbers are significantly worse than documented in older adults with HIV.[8] In one study of MSM of all ages, the percentage of those linked to HIV care within one month of diagnosis was lowest among AYA with HIV aged 13 to 19 (69%) and 20 to 24 (70%) years.[9] This group also had the lowest rates of retention in care and viral suppression. Older young adults (through age 29), who currently have the highest incidence of HIV infection among all age groups, have similar challenges, with 30% unaware of their infection status. They, too, require focused attention.

There are myriad reasons AYA with HIV do not perform as well on the HIV care continuum and are at greater risk of poorer clinical outcomes than adults with HIV. Perhaps most important, AYA with

HIV often do not have the same developmental capacity or ability to secure resources as their adult counterparts. These key features, discussed below, should be considered carefully because they can negatively affect HIV treatment and may alter clinical decision-making.

Adolescents and Young Adults with HIV as a Developmentally Distinct Patient Population

Developmental maturity in AYA with HIV generally can be grouped into several, often overlapping, areas, including physical, cognitive, communication and language, and social and emotional, combined with an emerging recognition of sexual identity. Several overarching factors—especially HIV-related stigma, discrimination, and a fear of familial and/or social rejection—can contribute to impaired development in all areas and adversely affect HIV treatment and clinical outcomes for many AYA with HIV. Additional important psychosocial factors discussed below commonly are seen in this population and also can affect development and successful HIV treatment.

Key developmental factors that may impact HIV treatment are highlighted below:

- ***Cognitive development:*** Evolving cognitive processes, which normally continue well into the third decade of life, are particularly relevant to HIV treatment in AYA with HIV. Their developing decision-making capacity often is driven by concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to fit in with their peers, all of which can affect HIV treatment negatively, including medication adherence and long-term clinical outcomes.[4,10,11] Likewise, AYA with HIV are at risk for neurocognitive impairment and mental health comorbidities,[12-15] including psychiatric, behavioral, and substance use disorders, which can further affect cognitive development and compromise effective HIV treatment.
- ***Physical development:*** The rapid physiologic changes (e.g., puberty, rapid growth) that occur in adolescence may result in altered ARV pharmacokinetics, underscoring the importance of adolescent-specific studies.[4] AYA with HIV, particularly those with infection acquired early in life and/or while sexually immature, also are at risk for impaired physical development, especially delayed sexual maturation and impaired normal bone development, which may have long-term consequences like reduced final height and peak bone mass, the latter being a key risk factor for developing osteoporosis.[16] Both delayed maturation and short stature may increase anxiety, depression, and stigma, which may, in turn, affect treatment adherence.[17] AYA with HIV who acquire HIV later in life still may be affected because peak bone mass is not achieved until around age 30. A small study showed lower bone mass in Tanner Stage 5 young men aged 20 to 25 years who acquired HIV during adolescence than in HIV-uninfected age-matched controls.[18]

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

Psychosocial and Related Risk Factors Affecting Adolescents and Young Adults with HIV

Several psychosocial, behavioral, and environmental risk factors affect many AYA with HIV and can undermine successful HIV treatment disproportionately in this population. Common key risk factors are summarized here:

- ***Mental and behavioral health:*** The percentage of AYA with HIV with behavioral and mental health conditions is very high and can undermine engagement in care and medication adherence. The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention deficit hyperactivity disorder. Among adolescents with

early-acquired HIV, nearly 70% meet criteria for a psychiatric disorder at some point in their lives.[13,19-21] Similarly, depression and anxiety were identified by symptom inventory 43% and 31% of the time, respectively, among AYA with HIV presenting for care at treatment sites in the Adolescent Trials Network.[22]

- ***Substance use:*** Substance use is prevalent among AYA with HIV. Among more than 2,000 AYA with HIV (72% acquiring HIV later in life) surveyed by the Adolescent Trials Network, weekly or more frequent use of tobacco (33%), marijuana (28%), alcohol (21%), and other illicit drugs (23%) was reported.[23,24] Young MSM had higher odds of each substance use behavior, whereas transgender women had increased odds of marijuana and other illicit drugs. Suboptimal ART was associated with increased risk of substance use behaviors,[24] underscoring the need to screen for and address substance use improve treatment outcomes.
- ***Transgender AYA with HIV:*** About 1 in 3 new HIV diagnoses among transgender individuals are among those aged 13 to 24 years.[25,26] Transgender AYA with HIV report high rates of stigma and other structural and logistical barriers that affect their access to gender-affirming care, as well as HIV prevention and treatment services, which are known to be associated with retention in care and adherence to treatment (see Transgender People with HIV).
- ***Homelessness and unstable housing:*** Among the 4.2 million homeless adolescents and young adults in the United States (of whom 700,000 are unaccompanied minors)[27] , the estimated HIV prevalence ranges from 3% to 16%. Youth who identify as lesbian, gay, bisexual, transgender, or queer (LGBTQ); those with mental health concerns; and those who engage in substance use are disproportionately represented among homeless youth.[28] Homeless and unstably housed AYA with HIV have greater difficulties securing and sustaining resources and engaging in and being retained in care and treatment.[29]
- ***Additional social and environmental factors:*** A number of social and environmental factors commonly found among AYA with HIV negatively affect their HIV treatment, including limited familial and/or social support, lack of health insurance and/or experience with health care systems, unstructured and chaotic lifestyles, transportation barriers, food insecurity, limited educational opportunities, limited employment opportunities and/or unstable employment, and a history of trauma and/or sexual abuse.[30]

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

Given the unique physiologic, developmental, and psychosocial characteristics discussed above, AYA with HIV require comprehensive systems of care with culturally competent providers and tailored treatment to serve all their specific medical and psychosocial needs. To maximize their chances of success, it is also imperative to routinely assess each AYA with HIV for individual factors that may need to be addressed or considered in treatment decisions or that may affect adherence.

Table 15 summarizes common adherence barriers among AYA with HIV, along with recommended support strategies. Refer to the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection and the Adherence to Antiretroviral Therapy in Children and Adolescents with HIV additional approaches. Targeted interventions to improve treatment effectiveness and adherence related to a few key psychosocial factors among AYA with HIV also are highlighted here:

- ***Mental health care:*** Strategies to improve the provision of mental health care for AYA with HIV are critically important for optimizing treatment for co-occurring HIV and mental health problems.[31] These strategies include improving provider education, integrating trauma-informed care practices, increasing access to mental health professionals through colocated services for HIV care, expanding care delivery paradigms like telemedicine, and optimizing treatment approaches. An example of the latter is a combination of tailored psychotherapy and pharmacotherapy.[26,32] Further guidance for providing appropriate mental health care for AYA with HIV can be found in the Pediatric Guidelines.
- ***Substance use disorders:*** Providers should assess and recommend treatment for substance use disorders, with consideration of emerging substance use trends, such as the use of electronic vapor products. Further guidance for providing appropriate substance use screening and treatment for AYA with HIV can be found in the Pediatric Guidelines and in the Substance Use Disorders and HIV section.
- ***Transgender AYA with HIV:*** Providers must increase their understanding of this population to minimize barriers and optimize testing, engagement, and outcomes for transgender AYA with HIV. Drug-drug interactions between hormonal therapy and ART can occur but are less common with newer ART regimens. Further information can be found in the Transgender People with HIV section and Adolescent Trials Network Transgender Youth Resources.[33]
- ***Psychosocial and environmental stressors:*** Multimodal interventions that enhance social support and teach adaptive coping skills may help AYA with HIV manage environmental stressors and improve clinical outcomes.

Specific Antiretroviral Therapy Considerations in Adolescents and Young Adults with HIV

All AYA with HIV should initiate ART as soon as possible and stay on ART indefinitely to maximize viral suppression, reduce morbidity and mortality, and prevent secondary HIV transmission **(AI)**. As described below, clinicians should consider simplifying ART regimens and using antiretrovirals with high barriers to resistance whenever possible to support adherence.

Strategies to Improve Medication Adherence

Clinicians selecting ART for AYA with HIV must balance the goal of prescribing a maximally potent regimen with a patient-by-patient assessment of existing and potential adherence barriers and available youth-friendly support strategies to facilitate adherence.[34] Additional considerations and strategies that may affect adherence among AYA with HIV are highlighted below in **Table 13.**

Table 13. Antiretroviral Therapy–Specific Strategies to Improve Medication Adherence

Antiretroviral Therapy-Specific Strategies to Improve Medication Adherence	
Regimen selection	• Simple ART regimens (e.g., fixed-dose, once daily combinations) with high barriers to resistance are preferable, if possible.[35] • Minimal side effects (e.g., gastrointestinal)
Treatment plan	• Develop the plan in partnership with AYA with HIV, considering daily schedule; tolerance of pill number, size, and frequency; issues affecting absorption; and potential adverse effects and interactions with other medications.[34,36] • Design adolescent-friendly reminder systems[37] (e.g., apps, cell phone reminders, pill boxes) for adherence support.[38]
Motivators	• Emphasize personal benefits (e.g., viral suppression, improved health). • Undetectable equals untransmittable (U=U) status disclosure to sexual partners without HIV may act as a particularly strong motivator for reducing stigma and improving adherence among AYA with HIV.

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

The boosted protease inhibitor (PI) darunavir (DRV) and the integrase strand transfer inhibitors (INSTIs) dolutegravir (DTG) and bictegravir (BIC) offer once-daily dosing. When coformulated with a dual nucleoside backbone, they also provide single-tablet regimens with high genetic barriers to resistance.

Clinical trials have demonstrated the superiority of DTG over boosted PI-based regimens. BIC coformulated with tenofovir (TAF) and emtricitabine (FTC) also appears to have a low risk of treatment-emergent resistance and is available as a single-tablet regimen with a small pill size and no food requirements. BIC is currently licensed for use in children or adolescents ≥25kg. Adolescent studies are ongoing with an adult fixed-dose combination of BIC/FTC/TAF from 12 years of age and 35 kg with a favorable interim analysis in a stable adolescent switch study.[39]

A two-drug once-daily single-tablet regimen of DTG/lamivudine is recommended as an initial ART regimen except for individuals with HIV RNA >500,000 copies/mL, hepatitis B virus (HBV) coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Long-acting formulation regimens, the first of which (cabotegravir/rilpivirine) was recently FDA-approved in the United States, are considered a viable option for patients who are engaged in care, virologically suppressed on oral therapy, and agreeable to the administration schedule. These agents are being studied for AYA with HIV[40] ages 12 to 17 without relevant antiretroviral drug resistance. Case reports of viral suppression with the use of long-acting rilpivirine (RPV) and cabotegravir (CAB)[41] in AYA with HIV with a history of poor adherence are encouraging (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression). Studies to evaluate these modalities among nonadherent AYA with HIV are under development.[42]

Antiretroviral Therapy–Experienced Adolescents and Young Adults with HIV with Drug Resistance

AYA with HIV who acquired HIV early in life often have treatment challenges associated with the long-term use of ART that mirrors those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects. In ART-experienced adolescents, DTG was safe and well tolerated, and it achieved viral suppression rates of 44% to 66% when combined with an optimized background regimen. Acquired treatment-emergent INSTI resistance may occur.[43] For adolescents with dual-class resistance, the introduction of DRV/cobicistat/FTC/TAF in combination with DTG offers the potential of a potent triple-class regimen with a high genetic barrier to resistance with only two pills once daily[44] (see Virologic Failure and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression).

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

The physiologic changes (e.g., puberty, rapid growth) that occur in adolescence may result in altered pharmacokinetics. Therefore, although generally it is appropriate for postpubertal adolescents to be dosed with ARV drugs according to adult guidelines, adolescents in early puberty should be dosed according to the Pediatric Guidelines, which factor in dosages by weight and sexual maturity ratings.

Additional Antiretroviral Therapy Considerations in Adolescents and Young Adults with HIV

Additional considerations include an increased risk of side effects, such as bone and renal toxicity with tenofovir-based drugs in the rapidly growing adolescent. These concerns are magnified in low-weight adolescents for whom appropriate lower-dose formulations are not available. Because AYA with HIV have not yet reached peak bone mass, TAF generally should be used instead of TDF, because of a greater bone loss with the latter ARV.

For a more detailed discussion on ART therapy in AYA with HIV, please see the What to Start section and the Pediatric Guidelines. For additional information on treatment adherence in AYA with HIV, please see Table 16, Adherence to the Continuum of Care, and the Pediatric Guidelines.

Preventive Measures and Supporting Long-Term Health in Adolescents and Young Adults with HIV

People with HIV are at an increased risk of HIV- and ART-related comorbidities, including cardiovascular disease, diabetes, metabolic syndrome, osteoporosis, and neurocognitive impairment. When HIV is acquired at birth or early in life, an individual can live for many decades with the condition. However, engagement in health-risk behaviors (e.g., tobacco smoking, alcohol and drug use, unhealthy diet, physical inactivity) may have greater long-term implications for clinical outcomes in this population.

Preventive health care and promotion of positive health behavior during the critical time of adolescence and young adulthood can shape future habits and clinical outcomes over a lifetime. Incorporating regular screening, preventive health care, and health education is critical for optimizing short- and long-term physical and mental well-being and should be considered part of routine HIV treatment. Careful attention should be paid to modifiable risk factors in these early decades, such as weight gain and obesity, dyslipidemia, vitamin D deficiency, and tobacco use. Aggressive screening

and risk factor mitigation early in the life of AYA with HIV not only improves current health but also can decrease their risk of developing comorbidities later in life. See HIV Medicine Association of the Infectious Diseases Society of America HIV primary care guidance for more details.

Transitioning to Adult HIV Care

Given lifelong infection with HIV and the need for treatment throughout the life course, HIV care programs and providers need flexibility to transition care appropriately for AYA with HIV. A successful transition requires an awareness of fundamental differences between many adolescent and adult HIV care models.

In most adolescent HIV clinics, care is more teen-centered and multidisciplinary, with primary care highly integrated into HIV care.[45] Often there is anonymity, with clinics not being devoted specifically to HIV or infectious diseases. Moreover, such services as sexual and reproductive health and mental health care are often found in one clinic setting (i.e., the medical home). Additionally, these clinics are more likely to be "youth-friendly" by including such aspects as waiting areas where AYA with HIV can access computers and other items that may facilitate engagement; flexible schedules that include evening hours or walk-ins; technology like social media and texting to engage patients; staff who are trained specifically in the unique cognitive, developmental, and other psychosocial aspects of AYA with HIV; and lower patient-to-provider ratios. In contrast, some adult HIV clinics may be more HIV-specific and rely more on referral of the patient to separate subspecialty care settings, such as gynecology.[46] Furthermore, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients.

Transitioning the care of an AYA with HIV must consider such factors as medical insurance; degree of independence, autonomy, and decision-making capacity; patient confidentiality; and informed consent. Nonetheless, given the structural limitations (adolescent clinics not being able to see patients over a certain age), care transitions must occur, usually between the ages of 21 and 25. The period of transition is a highly vulnerable time for attrition from HIV care. Data on transition outcomes are emerging, showing variable rates of successful transition to adult care ranging between 50% and 85%.[47-50]

It is important to recognize that the transition for AYA with HIV with early-acquired HIV versus those who acquired HIV later in life may pose distinct challenges. AYA with HIV who acquired HIV early in life—who often have experienced significant instability and prior loss—may experience the transition to adult HIV care as yet another traumatizing event. Alternatively, those who acquired HIV later in life, given their more recent engagement in the medical system, may be less likely to be effectively engaged in pediatric and adolescent care, which may affect their ability to transition successfully. Factors to date that have been associated with successful transition for those with early-acquired HIV include high self-management and perceived emotional and social support.[51]

To maximize the likelihood of a successful transition, interventions to facilitate transition are best implemented early on.[49,52-54] Strategies and approaches for both the adult and pediatric and adolescent programs are discussed below:

Table 14: Approaches to Optimize Care Transition for AYA with HIV

Pediatric/Adolescent	Adult
Personnel	
• Engage a multidisciplinary team knowledgeable about medical and psychosocial issues of AYA with HIV, including the challenges of transitioning youth to adult care settings. • Utilize combined internal medicine and pediatrics-trained providers if available. • Assign a transition point person and have their contact information readily available. • Educate HIV care teams and staff about transitioning AYA with HIV and their needs.	• Engage a multidisciplinary adult care team knowledgeable about medical and psychosocial issues of AYA with HIV, including the challenges of transitioning youth to adult care settings. • Utilize combined internal medicine and pediatrics providers if available. • Assign a transition point person and have their contact information readily available. • Identify outreach specialists, navigators, social workers, case managers, and providers with a youth-friendly approach. • Educate clinic personnel about AYA with HIV and their challenges to enhance sensitivity and understanding and minimize stigma.
Education and Preparation of AYA with HIV	
• Enhance AYA with HIV health literacy, including understanding of HIV and their medical history. • Address patient and family resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles. • Help youth develop life skills, including, but not limited to, counseling on appropriate use of a primary care provider and how to manage appointments; the importance of prompt symptom recognition and reporting; and self-efficacy in managing medications, insurance, and assistance benefits.	• Meet AYA with HIV before transition, if possible. • Clearly outline policies and expectations before and during the first visit. • Have an orientation plan to acquaint newly transitioned AYA with HIV to the clinic environment and adult clinical care program. • Implement interventions that may improve outcomes, such as patient navigators, peer support groups, mental health assessment, and inclusion of parents and guardians where available. • Address health literacy and ensure AYA with HIV understand HIV, goals of care, etc. • Continue to work with AYA with HIV toward developing life skills, etc.

Table 14: Approaches to Optimize Care Transition for AYA with HIV

Pediatric/Adolescent	Adult
Strategies and Approaches	
• Identify adult care providers able to provide youth-friendly care for adolescents and young adults. • Develop a formal, purposeful individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning to adult HIV care. • Optimize provider communication between adolescent and adult clinics, including a warm multidisciplinary, comprehensive medical history hand-off that includes prior regimens and outcomes (e.g., adherence, virologic failure and resistance).	• Develop a realistic clinic model based on specific needs (e.g., simultaneous transition of mental health and/or case management versus a gradual phase-in) and staffing. • Engage in a warm handoff from the pediatric team, which allows the accepting adult team to learn about and understand the multidisciplinary challenges and goals for the patient. Devise a plan for how to continue building the skills on the adult side. • Build in flexibility (e.g., permissive grace period for appointments, leniency for missed appointments, particularly when first transitioning). • Incorporate other aspects of care beyond HIV management, if possible (e.g., family planning, sexually transmitted infection testing and treatment, mental health, substance use).
Communication	
• Foster regular dialogue between pediatric and adolescent and adult teams before and after transition through regular meetings, case conferences, etc. • Solicit feedback from the AYA with HIV • Use technology (e.g., texting, HIPAA-compliant messaging apps, telemedicine).	
Evaluation	
• Implement ongoing evaluation to measure the success of the selected model (retention in adult care).	

Discussions regarding transition should begin early and before the actual transition process.[55] Attention to the key interventions noted above will be likely to improve adherence to appointments and avoid the potential for youth to fall through the cracks, as this concept is referred to commonly in adolescent medicine. For a more detailed discussion on specific topics related to transitioning care for adolescents and young adults, see Transitioning into Adult HIV Care. Please also refer to the Pediatric Guidelines.

Table 15: AYA with HIV ARV Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
Prioritization of short-term goals and socialization with peers over daily HIV treatment adherence	Youth-friendly reminder systems (e.g., text, phone, apps)	• Daily adherence to ARV regimens may not take priority in the lives of AYA with HIV. • AYA with HIV benefit from reminder systems to facilitate adherence.
	Novel ART delivery strategies (e.g., long-acting oral or injectable ARVs)	• AYA with HIV show interest in long-acting alternatives for ART delivery. • Long-acting ARVs are a promising tool to facilitate adherence, once approved for AYA with HIV.
Social concerns related to loss of confidentiality	Simple ARV regimens	• Adolescents do not want to be different from peers; adherence to complex regimens is particularly challenging. • Simple ARV regimens are preferable for AYA with HIV.
	User-friendly and discreet regimens	• Avoidance of HIV-related stigma and of unintentional disclosure of HIV status is a priority for AYA with HIV. • Protect confidentiality with user-friendly and discreet adherence supports (e.g., discreet pill bottles, reminder systems, etc.).
Side effects/fear of side effects	ARV regimens that minimize side effects	• Side effects are associated with nonadherence to ARVs. • Regimens with minimal side effects and medications that manage side effects have utility for AYA with HIV.
Denial or dismissal of HIV diagnosis	Motivational interviewing (MI) and motivational enhancement therapy (MET)	• MI and MET acknowledge AYA with HIV's autonomy and potential ambivalence about treatment adherence. • MI and MET have shown promise for improving adherence to chronic disease treatment, including HIV.
	Positive affirmation messages (e.g., text, app)	• Electronically delivered positive affirmation messages can improve self-esteem and ARV adherence among AYA with HIV.
Lack of health literacy regarding the benefits of ART	Health literacy support and U=U education	• AYA with HIV may not fully understand the importance of taking ARVs daily, particularly when they are asymptomatic. • Increased health literacy is associated with better adherence to ARV regimens. • U=U education holds promise for AYA with HIV.

Table 15: AYA with HIV ARV Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
Mistrust of providers and the medical establishment	Empathetic and patient-centered communication	• Communication exploring the needs of AYA with HIV patients can build trust, including exploring needs not directly related to HIV treatment (e.g., school, employment, relationships, etc.).
Mental health and/or substance use	Individualized mental health and substance use services	• Comprehensive mental health and substance use services have shown promise for improving viral suppression among AYA with HIV. • Service should be delivered based on individualized needs assessments.
	Directly observed therapy may be considered	• For some AYA with HIV with difficult adherence problems, directly observed therapy may be considered.
Lack of familial and social support	Family and peer support groups	• Family members and peers are a defense against stigma and social isolation, source of emotional support, and partners in medication management. • Family and peer support groups have utility for AYA with HIV living with HIV.
Provider views of AYA with HIV as "risky" and/or not ready for ART	Promote development of a positive rather than risk-centered identity among AYA with HIV	• Adolescence and young adulthood are periods of identity development where HIV stigma is particularly problematic. • Providers should not conceptualize AYA with HIV as "high risk" to reduce stigma and improve ARV adherence.
Provider implicit biases of AYA with HIV	Implicit bias training	• Consciously changing biased associations and repeated bias self-regulation training can reduce providers' implicit biases.
	Gender-affirming care	• Transgender individuals are more likely to achieve viral suppression when HIV care providers affirm their gender (e.g., use chosen name and pronoun). • For a more detailed discussion, see guidelines for Transgender People with HIV.

Table 15: AYA with HIV ARV Adherence Barriers and Strategies to Support Adherence

ART Adherence Barrier	Adherence Support Strategy	Rationale for Adherence Support Strategy
Lack of youth-friendly services	Dedicated youth HIV clinic	• Clinic days or hours dedicated to AYA with HIV patients better address unique adherence needs; youth-friendly services include the following: 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; and 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, e.g.: o offering evening hours; o staff training on service delivery to AYA with HIV; and 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; and o psychosocial support services (e.g., school support, transportation, support groups, housing and food assistance).
	Collaboration with and referrals to outside support services	• Where delivery of comprehensive supplemental services is not possible, collaborations with and referrals to outside support services should be considered.

Key: ART = antiretroviral treatment; ARV = antiretroviral; AYA = adolescent and young adult; U=U = undetectable equals untransmittable

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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, progression to AIDS and death will occur in the majority of individuals without treatment. • 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 initiation of ART (AIII). • HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; therefore, these drugs should not be included in ART regimens for HIV-2 infection (AII). • Patients with hepatitis B virus (HBV)/HIV-2 coinfection should be prescribed ART regimens that contain drugs with activity against both HIV-2 and HBV (AIII). • Initial ART regimens for ART-naive patients who have HIV-2 mono-infection or HIV-1/HIV-2 coinfection should include an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs) (AII). An alternative regimen is a boosted protease inhibitor (PI) that is active against HIV-2 (darunavir or lopinavir) plus two NRTIs (BII). • HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be used to assess treatment response (AIII). Unlike persons with HIV-1, persons with HIV-2 should continue to undergo periodic CD4 count testing even if their viral loads are persistently suppressed, because disease progression can occur despite an undetectable viral load. • Resistance-associated viral mutations to INSTIs, PIs, or NRTIs may develop in persons 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 ART regimen should be constructed in consultation with an expert in HIV-2 management.
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 persons of West African origin, persons who have had sexual contact with or who have shared needles with persons of West African origin, and persons 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 one million to two million individuals 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 have 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 HIV-1 and HIV-2 infection may occur, and the possibility of this coinfection should be considered when treating persons 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 persons 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 persons who have serologically confirmed HIV infection but who have 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 Food and Drug Administration (FDA) to differentiate HIV-1 infection from HIV-2 infection. The Multispot HIV-1/HIV-2 Rapid Test is no longer available. Commercially available HIV-1 RNA assays do not reliably detect or quantify HIV-2 RNA.[7] Quantitative HIV-2 RNA testing is available at the University of Washington (UW)[8] and the New York State Department of Health (NYSDOH).[9] HIV-2 nucleic acid amplification test-based (total DNA/RNA) diagnostic testing is available for clinical care at UW.[10] However, it is important to note that up to one-third of persons 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 persons 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 regimens for HIV-2 have been completed;[11] thus, the optimal treatment strategy has not been defined. Existing data on the treatment of HIV-2 and extrapolation from data on the treatment of HIV-1 suggest that ART should be started at or soon after HIV-2 diagnosis in order to prevent disease progression and transmission of HIV-2 to others **(AIII).** However, CD4 cell recovery in persons with HIV-2 who are on ART is generally poorer than that observed in persons with HIV-1.[12,13]

Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs); however, HIV-2 is more likely to develop resistance to NRTIs than HIV-1.[14] HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs);[15] thus, NNRTI-based regimens **are not recommended** for treatment of HIV-2 **(AII).** Several small studies in individuals with HIV-2 have reported poor responses to dual-NRTI

regimens[16,17] or regimens that contain an NNRTI plus two NRTIs.[18,19] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[20,21]

Integrase strand transfer inhibitor (INSTI)-based regimens or protease inhibitor (PI)-based regimens are treatment options for persons with HIV-2. As discussed below, two 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 plus TDF/FTC is currently underway (FIT-2; NCT02150993).

Integrase Strand Transfer Inhibitor-Based Regimens

All FDA-approved INSTIs—RAL, elvitegravir (EVG), dolutegravir (DTG), and bictegravir—have potent activity against HIV-2 *in vitro*.[22-26] INSTI-based regimens have shown favorable treatment responses in observational studies.[27-29] Two single-arm, open-label clinical trials have assessed the effectiveness of INSTI-based regimens in ART-naive individuals with HIV-2. One study evaluated RAL plus TDF/FTC, and the other evaluated EVG/cobicistat/TDF/FTC. Both studies demonstrated favorable clinical and immuno-virologic results at 48 weeks, providing the best evidence to date for HIV-2 treatment recommendations.[30,31]

Protease Inhibitor-Based Regimens

In general, regimens that contain boosted PIs that are active against HIV-2 (and that also include two NRTIs) have resulted in more favorable virologic and immunologic responses than regimens that consist of only two or three NRTIs.[12,13,21,32] Darunavir (DRV), lopinavir, and saquinavir are more active against HIV-2 than other approved PIs.[33-35] Older, unboosted PI-based regimens, including nelfinavir or indinavir plus zidovudine and lamivudine, and atazanavir-based regimens have shown poor clinical success rates.[11,16,17,36,37]

Amongst the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.[38] The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates;[39] 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.[40] There are no data yet on the activity of ibalizumab against HIV-2.

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection;[41-44] however, there are currently no comparative randomized controlled clinical trial data that support the effectiveness of a specific recommended regimen.

Until there are more definitive data on outcomes, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends the following regimens for 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 regimen for most individuals with HIV-2 **(AII).** Data from an observational study in Botswana suggest that there is an increased risk of neural tube defects in infants born to those who were receiving DTG at the time of conception; however, the risk of these defects is still low. Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.

- An alternative regimen is a boosted PI (DRV or LPV) that is active against HIV-2 plus two NRTIs **(BII).**
- NNRTI-based regimens **are not recommended** for persons with HIV-2 **(AII).**
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection require ART regimens that contain 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 cell counts, and clinical status should be monitored to assess treatment response, as is recommended for HIV-1 **(AII).**
- Persons 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 cell count and clinical monitoring. Unlike HIV-1, persons with HIV-2 require continued CD4 cell count monitoring, as disease progression can occur in the setting of undetectable HIV-2 viral load **(AIII).**

Persons with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as those 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.

Viral mutations that are associated with resistance to NRTIs, PIs, and/or INSTIs may develop in persons with HIV-2 while they are on ART.[35,45,46] Currently, transmitted drug resistance appears to be rare among people with HIV-2.[47,48] In several small studies, twice-daily dosing of DTG was found to have some residual activity as a second-line INSTI in some persons with HIV-2 who had extensive ART experience and RAL resistance.[49-52] 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).[53] 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 Persons with HIV
• Antiretroviral therapy (ART) is recommended for all people with HIV regardless of CD4 T lymphocyte cell count (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. • Given that the burden of aging-related diseases is significantly higher among persons with HIV than in the general population, additional medical and social services may be required to effectively manage both HIV and comorbid conditions. • Adverse drug events from ART and concomitant drugs may occur more frequently in older persons 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. • Polypharmacy is common in older persons with HIV; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and concomitant medications. Potential for drug-drug interactions should be assessed regularly, especially when starting or switching ART and concomitant medications. • The decline in neurocognitive function with aging is faster in people with HIV than in people without HIV. HIV-associated neurocognitive disorder (HAND) is associated with reduced adherence to therapy and poorer health outcomes including increased risk of death. For persons with progressively worsening symptoms of HAND, referral to a neurologist for evaluation and management or a neuropsychologist for formal neurocognitive testing may be warranted (BIII). • Mental health disorders are a growing concern in aging people with HIV. A heightened risk of mood disorders including anxiety and depression has been observed in this population. Screening for depression and management of mental health issues are critical in caring for persons with HIV. • HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older persons with HIV and complex comorbidities. • Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of older 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

Effective antiretroviral therapy (ART) has increased survival in individuals with HIV,[1, 2] resulting in an increasing number of older individuals living with HIV. In the United States, from 2012 through 2017, the annual fraction of persons newly diagnosed with HIV aged ≥50 years was stably 17%.[3] Among persons with HIV at year-end 2016, 48% were aged ≥50 years, 8% were aged ≥65 years, and trends suggest that these proportions will increase steadily.[3] Care of people with HIV will increasingly involve adults aged ≥60 years, a population for which data from clinical trials or pharmacokinetic (PK) studies are very limited. The discussion in this section of the guidelines refers to individuals aged ≥50 years as older persons with HIV.

There are several distinct areas of concern regarding aging and HIV.[4] First, older persons with HIV may suffer from aging-related comorbid illnesses and require substantially more non-ART medications[5] than younger people, which may complicate HIV clinical care.[6] Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of clinical syndromes generally associated with more advanced age. Third, reduced mucosal and immunologic defenses (e.g., postmenopausal atrophic vaginitis) 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) in older adults may lead to increased risk of acquisition and transmission of HIV.[7, 8] Finally, HIV screening among older adults remains low because they are generally perceived to be at low risk of acquiring HIV.

HIV Screening and Diagnosis in the Older Person

Failure to consider a diagnosis of HIV has likely contributed to later initiation of ART in older persons with HIV.[9] The Centers for Disease Control and Prevention (CDC) estimates that in 2016, 36% of adults aged ≥55 years met the case definition for AIDS at the time of HIV diagnosis. The comparable CDC estimates are 16% for adults aged 25 to 34 years and 27% for adults aged 35 to 44 years.[10] In one observational cohort, older people (defined as those aged ≥35 years) appeared to have lower CD4 T lymphocyte (CD4) cell counts at seroconversion and steeper CD4 count decline over time,[11] and tended to present to care with significantly lower CD4 counts.[12] When individuals aged >50 years present with severe illnesses, HIV and AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Although many older individuals engage in risk behaviors associated with acquisition of HIV, they may see themselves or be perceived by providers as at low risk of infection and, as a result, they are less likely to be tested for HIV infection than younger persons.[13, 14] Despite CDC guidelines recommending HIV testing at least once for individuals aged 13 to 64 years, and more frequently for those at risk,[15] HIV testing prevalence remains low (<5%) among adults aged 50 to 64 years, and decreases with increasing age.[16] Clinicians must be attuned to the possibility of HIV infection in older adults, including those aged ≥64 years, especially in those who may engage in high-risk behaviors. Sexual history taking and screening for other risk factors (e.g., injection drug use) that may place older adults at risk of HIV infection are therefore an important component of general health management for older adults. Risk-reduction counseling, and screening for HIV and sexually transmitted infections should be done, if indicated. Older adults who are at risk of acquiring HIV should be counseled on comprehensive HIV prevention strategies, including the option of HIV pre-exposure prophylaxis (PrEP). Age alone should not exclude older adults from being evaluated for and offered PrEP (refer to CDC PrEP Guidelines for details).

Impact of Age on HIV Disease Progression

HIV infection in older persons presents unique challenges and these challenges may be compounded by ART:

- Chronic HIV infection is associated with elevated cellular and soluble markers of immune activation and inflammation. Although these levels decline with ART, they remain higher than normal, even with suppressive ART. Levels of these markers also increase with aging, and the rate of this age-related change was demonstrated to be faster in people with HIV with viremia than in those with virologic suppression on ART and in people without HIV.[17]

- HIV infection may induce immuno-phenotypic changes akin to accelerated aging, with senescent T cells which in older persons have been associated with negative outcomes including frailty and cardiovascular disease.[4,18-21] Some studies have shown that people with HIV may exhibit chromosomal and immunologic features similar to those induced by aging, such as the accumulation of highly differentiated $CD28^-/CD57^+$ $CD8^+$ T cells commonly used as markers of immunosenescence.[22-24] However, other studies show the immunologic changes in HIV to be distinct from age-related changes.[25] Cytomegalovirus (CMV) infection is very prevalent among people with HIV, and as they age, immune response to CMV—rather than HIV—may play a pivotal role in immunosenescence observed even in people with virologic suppression.[26]
- Although data on the increased incidence and prevalence of age-associated comorbidities in people with HIV are accumulating,[27,28] the age at diagnosis for myocardial infarction, stroke, and non-AIDS cancers in people with and without HIV is the same.[28,29]
- As the life expectancy of persons living with HIV increases with ART, more cisgender women with HIV are experiencing menopause. Although menopause may occur earlier in cisgender women with HIV than in cisgender women in the general population,[30] early menopause may also be a consequence of smoking, depression, substance use, and other psychosocial factors that are disproportionately present in cisgender women with HIV.[31]
- Older persons with HIV have a greater incidence of health complications and comorbidities than adults of a similar age who do not have HIV, and may exhibit a frailty phenotype (defined clinically as a decrease in muscle mass, weight, physical strength, energy, and physical activity) earlier and in greater proportions than the general population.[32,33] Frailty in persons with HIV has been associated with adverse outcomes including incident cardiovascular disease, diabetes mellitus, recurrent falls and fractures, lower quality of life scores, cognitive impairment, hospitalization, and mortality.[34-43] Cisgender women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.[34, 44-46] Although the frailty phenotype is still incompletely characterized in people with HIV, its early recognition may lead to targeted interventions to improve the wellbeing of this population.[43]

Antiretroviral Therapy in the Older Person with HIV

Importance of Early Treatment Initiation

ART is recommended for all individuals with HIV (**AI;** see Initiation of Antiretroviral Therapy). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population.[47,48] 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).[49] This was 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 to70 years.[50] It was also seen in a START substudy in which persons aged >50 years were among the groups that experienced the greatest risk reduction when ART was started when CD4 counts were >500 cells/mm^3.[51] All older persons 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.

Choice of Antiretroviral Regimens in the Older Person with HIV

The choice of antiretroviral (ARV) regimen for an older person with HIV should be informed by a comprehensive review of the person's other medical conditions and medications. 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, osteoporosis). In older persons with HIV and reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix B, Table 11). In addition, ARV regimen selection may be influenced by potential interactions between ARV medications and drugs used concomitantly to manage comorbidities (see Tables 24a-25b). Adults aged >50 years should be monitored for ART effectiveness and safety as similarly recommended for other populations with HIV (see Table 3); however, in older persons, 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). ART regimens that contain tenofovir disoproxil fumarate (TDF), boosted protease inhibitors (PIs), or both are associated with a significantly greater loss of bone mineral density than regimens containing other NRTIs and integrase strand transfer inhibitors (INSTIs).[52-55] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide may be considered as alternatives to the use of TDF in older individuals who may be at risk of osteopenia or osteoporosis; however, with ABC, the benefit should be balanced with potentially increasing risk of cardiovascular disease.

Antiretroviral Efficacy and Safety Considerations in the Older Person with HIV

The efficacy, PKs, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART differs in older and younger people. In an observational study, a higher rate of viral suppression was seen in people aged >55 years than in younger people.[56] However, ART-associated CD4 cell recovery in older adults is generally slower and lower in magnitude than in younger people;[12,57-59] suggesting that starting ART at a younger age may result in better immunologic response and possibly clinical outcomes.

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.[60] 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 unknown whether drug accumulation in the older person may lead to greater incidence and severity of adverse effects than seen in younger persons, therapy in older persons requires close monitoring and heightened awareness of drug-related adverse outcomes.

Impact of Comorbidities and Polypharmacy in Older Persons with HIV

People with HIV and aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management.[5] In addition to taking medications to manage HIV infection and comorbid conditions, many older persons 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 persons with HIV than similarly aged persons in the general population.[5,61-63] In one large cohort of older patients with HIV in France, 62% of those whose HIV was diagnosed before 2000 had one or more comorbidities, and 70% were receiving at least one comedication.[64] Among persons living with HIV aged ≥65 years, the prevalence of comorbidities and polypharmacy rose with increasing age and duration of HIV infection.[65]

In older persons without HIV, polypharmacy is a major cause of iatrogenic complications.[66] Some of these complications may be caused by medication errors (by prescribers or patients), medication nonadherence, additive drug toxicities, and drug-drug interactions. Older persons 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 complaint or laboratory abnormality in people with HIV, especially in older persons, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

Drug-Drug Interaction Concerns

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.[67] Potential drug-drug interactions can occur between ARV and non-ARV medications, as well as between non-ARV medications.[63] The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young participants with normal organ function who do not have HIV (see Tables 24a-25b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of an interaction may be greater in older persons with HIV than in younger people with HIV; therefore, it is very important to remain vigilant to potential drug-drug interactions given the high prevalence of polypharmacy in older persons with HIV. In reviews of ARV and non-ARV medications prescribed for older persons with HIV, more than half of the medications had the potential for drug-drug interaction, including some severe interactions.[68,69] The risk appears to be higher with PI-based ART than with INSTI-based ART.[68-70]

Adherence Concerns

Suboptimal adherence to ART is the most common cause of treatment failure. Complex dosing requirements, high pill burden, polypharmacy, inability to access medications because of cost or availability, limited health literacy (including misunderstanding of instructions), depression, and neurocognitive impairment are among the key reasons for nonadherence.[71] Although many of these factors associated with nonadherence may be more prevalent in older persons with HIV, some studies have shown better adherence to ART among older persons than younger individuals.[72-74] Severe menopausal symptoms are also associated with reduced adherence to ART, which increases the risk of drug resistance and adverse HIV-related health outcomes in menopausal cisgender women.[75] Clinicians should regularly engage with older persons to identify any factors, such as neurocognitive deficits or hormonal changes, that may decrease adherence to ART. To facilitate medication adherence, it may be useful to discontinue unnecessary medications, simplify regimens, and recommend evidence-based behavioral approaches including the use of adherence aids such as pillboxes or daily calendars, and support from family members (see Adherence to the Continuum of Care).

Optimizing Antiretroviral Therapy in Older Persons 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 and drug-drug interactions. For example, expert guidance now recommends bone density monitoring in men aged ≥50 years and postmenopausal cisgender women, and suggests switching from TDF or boosted PIs to other ARVs in older persons at high risk for fragility fractures.[76] Given the high prevalence and faster progression of chronic kidney disease in aging persons with HIV, likely from a combination of HIV, ART, and non-HIV risk factors, development of the disease in an older person on ART must be monitored with great vigilance.[77,78] In persons with HIV at risk for or with declining renal function, consideration should be given to avoiding regimens containing TDF and atazanavir.[79]

Interrupting or Discontinuing Antiretroviral Therapy in Older Persons with HIV

Few data exist on the use of ART in severely debilitated people with chronic, severe, or non-AIDS-related terminal conditions.[80,81] Withdrawal of ART usually results in rebound viremia and a decline in CD4 count. In addition, an acute retroviral syndrome after abrupt discontinuation of ART has been reported. Even in severely debilitated adults, most clinicians would continue therapy 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 patient and/or family members after a discussion of the risks and benefits of continuing or withdrawing treatment.

Non-AIDS HIV-Related Complications and Other Comorbidities in the Older Person with HIV

As AIDS-related morbidity and mortality have decreased among persons treated effectively with ART, non-AIDS conditions constitute an increasing proportion of serious illnesses among people with HIV.[82-84] The burden of age-related diseases is significantly higher among persons with HIV than in the general population, likely due to both traditional non-HIV-related and HIV-related factors.[85] Heart disease and cancer are the leading causes of death in older Americans.[86] 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. Moreover, people with HIV are more likely to be current or former cigarette smokers than adults without HIV,[87] and model-based analyses have suggested that smoking cessation could improve life expectancy among older adults with HIV on ART.[88]

The prevalence of multimorbidity among persons with HIV has increased in the past decade,[89] with hypertension and hypercholesterolemia being the most common comorbidities. The presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection may add to the disease burden of aging among adults with HIV.[90-92]

HIV-specific primary care guidelines have been developed and are available for clinicians caring for older persons with HIV.[93,94] Specific guidelines have also been developed for the evaluation and management of the following specific comorbidities in people with HIV: bone health,[76] kidney disease,[95] and cardiovascular disease.[96] In addition, the following guidelines recently developed for the general population can be applied to the older persons with HIV: management of hyperglycemia[97] and hyperlipidemia.[98] However, it is important to note that the recommendations in 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 persons with HIV.[99]

Neurocognitive Impairment and Mental Health Concerns in the Older Person with HIV

HIV-associated neurocognitive disorder (HAND), manifesting as difficulty with memory, attention, speed of information processing, and executive and motor functions, affects up to 30% of people with HIV on virally suppressive ART.[100] Though an accurate prevalence of neurocognitive impairment in older people with HIV is not yet available, the risk of HIV-associated brain injury and HAND appears to be higher with increasing age.[101-103] Neurocognitive function declines with increasing age in people with or without HIV, but the trajectory of the decline is steeper in individuals with HIV.[104] This accelerated decline is likely multifactorial, relating to injury associated with direct HIV effects in the brain, higher prevalence of comorbidities and coinfections, more severe vascular disease, mental health disorders, social isolation, and polypharmacy in this population.[105-107] Hormonal shifts that occur with aging may contribute to neurocognitive impairment, and these changes may manifest as unique differences in clinical manifestations by gender.[108] Finally, the risk of neurodegenerative disease rises with increasing age independent of HIV, and differentiating HAND from Alzheimer's disease or other forms of progressive dementia is now an important clinical concern.[109]

HAND carries potentially detrimental clinical consequences for aging people with HIV. In a prospective observational study, neurocognitive impairment was predictive of lower likelihood of retention in care among older persons.[110] HAND is also associated with reduced adherence to therapy[111] and poorer health outcomes including increased mortality.[112] Given the importance of cognitive health, screening for neurocognitive impairment is important, though optimal primary-care based screening methods are as yet unclear. Initial screening with questions regarding any symptoms of memory or concentration difficulties should be performed routinely, though individuals with substantial impairment may not have enough insight into their condition to answer the questions. No brief cognitive screening test has been clearly shown to be sensitive or specific for HAND; the frequently used Mini-Mental State Exam does not typically capture executive function impairment which is the main manifestation of subtle HAND.[113] The Montreal Cognitive Assessment may be more sensitive for HAND but is not specific. If a patient 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)**.

Mental health disorders 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 individuals, a heightened risk of mood disorders including anxiety and depression was noted among those with HIV.[114] Social isolation combined with depression is particularly common among older adults with HIV and, in addition to its direct effects on morbidity and mortality, may contribute to poor medication adherence and retention in care.[115,116] The risk of suicide remains greater in people with HIV than in the general population, though increasing age may not further heighten the risk.[117] 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, and group therapy, and often pharmacological treatment.[118,119] 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, Cost Sharing, and End-of-Life Issues

The significantly increased burden of age-related comorbidities, including cardiovascular disease, chronic kidney disease, neurocognitive disease, and fractures, leads to a considerable increase in healthcare utilization and higher costs.[120] 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. The increased life expectancy and higher prevalence of chronic complications in aging populations with HIV can place greater demands upon HIV services[121] and require a focused approach to prioritize modifiable health-related problems.[122] Facilitating continued access to insurance can minimize treatment interruptions and reduce the need for other services to manage concomitant chronic disorders. As with all aging people, it is important to discuss living wills, advance directives, and long-term care planning.

Conclusion

HIV infection can be overlooked in aging adults who tend to present with more advanced disease and experience accelerated CD4 loss. HIV induces immune-phenotypic changes that have been compared to accelerated aging. Effective ART has prolonged the life expectancy of people with HIV, increasing the number of adults aged >50 years living with HIV. However, unique challenges in this population include greater incidence of health complications and comorbidities, some of which may be exacerbated or accelerated by long-term use of some ARV drugs. Providing comprehensive multidisciplinary medical and psychosocial support to patients and their families (the “Medical Home” concept) is of paramount importance in the aging population. Continued involvement of HIV experts, geriatricians, and other specialists in the care of older persons with HIV is warranted.

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Substance Use Disorders and HIV

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Key Considerations and Recommendations
• Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care (AII). • The most commonly used substances among people with HIV include alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. • Health care providers should be nonjudgmental when addressing substance use with their patients (AIII). • People with HIV and SUDs should be screened for additional mental health disorders (AII). • People with HIV and SUDs should be offered evidence-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment; see Table 13 below) as part of comprehensive HIV care in clinical settings (AI). • Ongoing substance use is not a contraindication to antiretroviral therapy (ART) (AI). People who use substances can achieve and maintain viral suppression with ART. • Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors), the potential for drug-drug interactions, and the risk or severity of substance-associated toxicities (e.g., increased hepatotoxicity or an increased risk of overdose). • Selection of antiretroviral (ARV) regimens for individuals who practice unhealthy substance and alcohol use should take into account potential adherence barriers, comorbidities that could impact care (e.g., advanced liver disease from alcohol or hepatitis viruses), potential drug-drug interactions, and possible adverse events associated with the medications (AII). • ARV regimens with once-daily dosing of single-tablet regimens, high barriers to resistance, low hepatotoxicity, and low potential for drug-drug interactions are preferred (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Background on Substance Use Disorders Among People with HIV

Ending the HIV epidemic requires addressing substance use among people with HIV, which poses a barrier to optimal engagement in the HIV care continuum. Ongoing substance use may prevent an individual from being tested for HIV, initiating antiretroviral therapy (ART), or adhering to ART, and it may increase the frequency of behaviors that put a person at risk for HIV transmission. Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors, needle sharing, and injection of substances), the potential for drug-drug interactions, and the risk or severity of substance-related toxicities (e.g., increased hepatotoxicity and increased risk of overdose). In the United States, the death toll for drug overdose (70,237 deaths in 2017)[1] now far exceeds the death toll for HIV (15,807 deaths in 2016).[2] As the drug overdose epidemic continues to expand, health care providers need a basic understanding of how to screen for and treat substance use disorders (SUDs) in people with HIV in clinical settings.[3]

Substance use exists on a continuum from episodic use to a 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 "hazardous drinking." A comparable category does not exist for other substances. The prevalence of substance use and SUDs is higher among people with HIV than among the general public,[4] and polysubstance use is common. This section will focus on the most commonly used substances among people with HIV: alcohol, benzodiazepines, cannabinoids, club drugs,[5] opioids, stimulants (cocaine and methamphetamines), and tobacco.

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 ("chemsex"). This research highlights the impact of substance use on sexual risk behaviors; although no precise definition of "chemsex" exists, studies have investigated the use of many different 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 patients) had higher odds of acquiring new HIV infection, bacterial sexually transmitted infections (STIs), and/or hepatitis C virus (HCV).[6] A much larger analysis using the European Men Who Have Sex with Men (MSM) Internet Survey, which collected data from 16,065 United Kingdom–based respondents, found that MSM who reported using methamphetamines or gamma-hydroxybutyrate (GHB) during the previous year were more likely to have gonorrhea infection than MSM who did not use these drugs, with odds ratios of 1.92 and 2.23, respectively.[7] These data emphasize the need to screen patients for substance use and STIs in clinical settings.

Screening for Substance Use Disorders

Screening for SUDs should be incorporated into the routine clinical care of all people with HIV. The following questions can be used to screen for drug or alcohol use: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" and "How many times in the past year have you had X or more drinks in a day?" (X is five for men and four for women).[8] Data are lacking on the appropriate threshold for alcohol use among transgender individuals, so until data clarify the risks, providers should use the more conservative threshold of four drinks. Individuals with liver disease, including active HCV infection, should not consume alcohol. A positive response at least one time on either screen should prompt additional screening with other short yet effective screening tools (see the Screening and Assessment Tools Chart from the National Institute on Drug Abuse). These tools can identify substance use and guide decisions on appropriate treatment interventions. Currently, not enough data exist to determine how often patients 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 their patients. Patients who experience stigma or who feel judged may not trust the health care provider's recommendations, may avoid returning to see that provider again, and may consequently have poorer health outcomes.[9] Language is one way in which stigma is communicated, and words such as

"addict" and "dirty urine" convey a negative connotation. The Office of National Drug Control Policy (ONDCP), American Medical Association, American Society of Addiction Medicine, International Society of Addiction Journal Editors, and others have recommended the adoption of clinical, non-stigmatizing language for substance use, as described in the "Changing the Language of Addiction" report from ONDCP.

Co-Occurring Mental Illness

Many people who use substances have co-occurring mental health disorders, including a history of trauma that may drive or exacerbate their substance use. Conversely, ongoing use of substances can place individuals at risk of trauma, such as sexual assault and sexual exploitation, which may further exacerbate their substance use.[6,10] People with SUDs should undergo evaluation and treatment for concurrent mental health disorders using standardized screening instruments (e.g., the Patient Health Questionnaire-2 [PHQ-2] for depression). Where applicable, clinicians should use available behavioral and pharmacological interventions to address mental health concerns, because recommending that patients stop their substance use without providing treatment for underlying mental health conditions has very limited efficacy.[11]

Several behavioral interventions have shown promise in randomized trials. Motivational interviewing, cognitive behavioral therapy, or a combination of the two have led to decreases in stimulant use, decreases in risky sexual behaviors, and improved adherence to ART.[12] Contingency management, a behavioral intervention that provides rewards for abstinence, has been shown to be effective in decreasing stimulant use among people with HIV, but whether decreases in stimulant use are sustained over time is less clear.[13]

Selecting, Initiating, and Maintaining Antiretroviral Therapy

Ongoing substance use is not a contraindication to having ART prescribed. Indeed, ART reduces the risk of HIV transmission to sexual partners and to individuals who share drug paraphernalia. These clinical, community, and individual benefits should encourage health care providers to initiate ART in people with HIV who use substances and those with SUDs.

When selecting antiretroviral (ARV) regimens for individuals who use substances, clinicians should consider potential barriers to adherence (see Adherence to the Continuum of Care), co-morbidities that could impact care (e.g., advanced liver disease from alcohol or HCV), potential drug-drug interactions, and possible adverse events that are associated with the medications. Providers should discuss adherence with their patients during multiple, nonjudgmental evaluations. In general, the use of simplified ARV regimens should be considered to aid ART adherence. Regimens for people with SUDs should be easy to take, such as a once-daily, single-tablet regimen,[14] and should have a high barrier to resistance or a low risk of hepatotoxicity. Adherence counseling should highlight the benefits of ART use, irrespective of concurrent substance use. Additionally, a reduction in substance use may improve adherence to ART.[15]

The development of long-acting injectable (LAI) antiretrovirals provides additional options for patients on ART. The combination of injectable cabotegravir (CAB) and rilpivirine (RPV) is an optimization option for patients who demonstrate retention in HIV care and who are virologically suppressed on oral therapy (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression). Current research on these medications is limited to individuals with expected good adherence and an ability to achieve virologic suppression on oral therapy prior to starting LAIs. To

date, little research has examined the use of these medications to support individuals struggling with adherence. Specifically, data on the use of CAB and RPV to improve medication adherence for people who actively use substances or have SUDs are lacking. LAI anti-psychotics have been studied in people with schizophrenia and SUDs. Starr and colleagues, for example, found fewer treatment failures using a once-a-month injectable paliperidone when compared to an oral anti-psychotic regimen.[16] The use of LAIs, however, presents unique concerns in people with HIV and SUDs, given the potential for the emergence of HIV drug resistance in the case of reduced adherence to or a delay in receiving scheduled injections.

The following factors should be considered when contemplating the use of LAIs in people with HIV and SUDs:

- As with all treatment conversations, providers should discuss adherence with their patients during multiple, nonjudgmental evaluations.
- Providers and people with HIV should consider the impact of using LAIs in the context of current or past substance use behaviors. Although some people may welcome or even prefer LAIs,17 one qualitative study highlighted that some people who either currently inject or previously injected substances may find that LAIs are a trigger for the injection of illicit substances.[18]
- Studies utilizing LAIs have included individuals with good adherence before starting the LAIs, but this should not exclude people with SUDs who are struggling with adherence from being considered for LAIs. Rather, the clinical team should consider what additional support may be needed to help people with SUDs be successful with LAIs. Some people with HIV may benefit from the administration of LAI in conjunction with methadone for the treatment of opioid use disorder, given anticipated adherence with methadone clinic visits. Case management, patient navigators, and/or peer navigators should be considered to help patients return for follow-up injections.
- Given the often unpredictable lifestyles of people with SUDs, clinical care teams should be flexible in scheduling patients for injections or accommodating walk-ins for injections.
- Patients with hepatitis B virus (HBV) have not been studied with CAB and RPV because these patients would need oral agents for HBV treatment. People with HIV should be screened for HBV infection and vaccinated before consideration of CAB/RPV, if not already immune or infected.
- Depressive disorders have been associated with CAB and RPV, so patients with SUD should be screened for depressive disorders and treated for depression if indicated. If depressive disorders worsen while on CAB and RPV, patients should be reevaluated to determine whether continued therapy with this regimen is advisable.

Importantly, multiple knowledge gaps exist regarding the use of LAIs among people with HIV and SUDs. The results from the ongoing Long-Acting Therapy to Improve Treatment Success in Daily LifE (LATITUDE) Study (NCT 03635788) will provide needed information on using LAIs among people with HIV and SUDs who have struggled with ART adherence.[19] Additional research is needed to determine optimal methods to support ART adherence (including LAI adherence) 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, etc.) and the appropriate individual interventions needed to support overall ART adherence.

Commonly Used Substances and Their Impact on HIV and Antiretroviral Therapy

Health care providers should have a basic understanding of evidence-based treatments for different substances, including alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. The sections below discuss the impact of these substances on people with HIV and how these substances affect ART use.

Alcohol

Epidemiology

Alcohol consumption is common among people with HIV. Recent estimates indicate that >50% of people with HIV in the United States consume any amount of alcohol (range, 54%–67%).[20,21] 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 Alcohol Use Disorders Identification Test-Consumption (AUDIT-C).[21] Unhealthy alcohol use includes a spectrum of consumption, including risky or hazardous use, heavy episodic use (binge drinking), and alcohol use disorder (AUD).[22]

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.[23-25] In a meta-analysis of 27 studies, any alcohol use, unhealthy alcohol use, and alcohol use in sexual contexts all were associated with condomless sex among people with HIV.[24]

In addition, unhealthy alcohol use has been associated with interruptions in all steps of the HIV care continuum, including lower adherence to ART.[26,27] 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.[28-30] 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.[31-33] Studies also have demonstrated an association between unhealthy alcohol use and the loss of durable viral suppression,[34,35] greater time spent with a viral load >1,500 copies/mL after ART initiation,[36] increased risk of viral rebound, lower retention in care,[37,38] and increased mortality.[39-41] 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.[42,43] Finally, in general medical populations, unhealthy alcohol use complicates the management of diabetes mellitus, hypertension, mental health disorders, other substance use, and other chronic diseases, and it increases the risk for pneumonia, osteoporosis, a number of cancers (e.g., liver, head and neck, and breast cancers), and tuberculosis.

Management of Unhealthy Alcohol Use

Ongoing alcohol use is not a contraindication for a person to receive ART. However, treatment for unhealthy alcohol use may improve HIV treatment outcomes. Behavioral treatments for unhealthy alcohol use among people with HIV demonstrate a small but significant reduction in alcohol use[44]

(see additional resources for alcohol management from the National Institute on Alcohol Abuse and Alcoholism and the Substance Abuse and Mental Health Services Administration [SAMHSA]). Pharmacotherapy also can reduce alcohol use among people with HIV. The Food and Drug Administration (FDA) has approved three pharmacotherapies for AUD: naltrexone, disulfiram, and acamprosate (see Table 13 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,[45,46] 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. In a randomized placebo-controlled trial of 100 prisoners with HIV who met the criteria for AUD, individuals who were provided depot naltrexone upon release from prison were more likely to achieve viral suppression at 6 months than the placebo group (56.7% versus 30.3%).[46]

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 patients who receive alcohol treatment medication, counseling, and formal outpatient alcohol treatment services. Integrating these treatments also may improve the likelihood that a patient will achieve viral suppression on ART. A randomized controlled trial of 128 individuals with HIV and AUD compared an integrated stepped-care model of alcohol treatment in Veterans Administration HIV clinics to treatment as usual. At the end of treatment (24 weeks), integrated stepped care resulted in more participants' receiving pharmacotherapy for AUD and participating in counseling. Although differences in alcohol use and viral suppression were not seen at 24 weeks, at 52 weeks, integrated stepped care was associated significantly with an increased number of alcohol-abstinent days, a decrease in the number of drinks per drinking day, and a decreased number of heavy drinking episodes. In addition, the patients in the stepped care group had increased odds of achieving viral suppression (odds ratio [OR] 5.58; 95% confidence interval [CI], 1.11–27.99).[47]

Liver cirrhosis—whether related to chronic heavy alcohol use, viral hepatitis, or nonalcoholic fatty liver disease—can result in altered metabolism of ARV drugs. For those who have hepatic impairment due to alcohol-related liver disease, ART dosing should follow the recommendations in Appendix B, Table 10, which are based on Child-Pugh classifications.

Benzodiazepines

Epidemiology

A specific epidemiologic data on the prevalence of benzodiazepine use among people with HIV are limited, the use of benzodiazepines can impact both morbidity and mortality. 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.[48]

Risk-Taking Behaviors and the HIV Care Continuum

People who inject drugs and who also use benzodiazepines engage in riskier behaviors than people who inject drugs but do not use benzodiazepines; these behaviors may include paying for sex,

sharing injection equipment with more people, and performing more frequent injections.[49] 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.[50] 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.[51] Benzodiazepines also are used illicitly to counteract the negative side effects of stimulants, such as cocaine and methamphetamine.[52]

Management of Benzodiazepine Use

Repeated use of benzodiazepines can result in physiologic dependence and life-threatening withdrawal in some patients. When feasible, individuals who chronically take benzodiazepines should be slowly tapered off the benzodiazepines under the supervision of an experienced clinician. Different benzodiazepines have different potencies (e.g., alprazolam is more potent than diazepam) and, therefore, require different tapers in terms of length and graduated decrease in dosage.

Benzodiazepine and Antiretroviral Drug Interactions

Several pharmacological interactions with ARV drugs also have been described. For example, some benzodiazepines are cytochrome P (CYP) 3A4 substrates; thus, when these benzodiazepines are used with a ritonavir-boosted or cobicistat-boosted ARV drug, their half-lives and concentrations can increase significantly, leading to enhanced and prolonged sedating effects. See Drug–Drug Interactions for available data on benzodiazepine-related interactions.[53]

Cannabis and Cannabinoids

Epidemiology

Both medical and recreational cannabis (marijuana) use are prevalent among people with HIV.[54] Cannabis belongs to a class of compounds that activate cannabinoid receptors. This class, known as cannabinoids, also includes synthetic compounds, such as K2. In recent years, cannabinoids have become more popular. In 2009, two cannabinoids were reported to the National Forensic Laboratory Information System. By 2015, 84 compounds had been reported.[55] These compounds most commonly cause tachycardia, agitation, and nausea, but they have a wide range of psychiatric effects, including psychosis and paranoia.[56]

Risk-Taking Behaviors and the HIV Care Continuum

Cannabis has not been shown to negatively impact adherence to ART or a patient'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.[57] 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.[58] In some cases, however, cannabinoids have been listed as the cause of death in overdoses. While data are lacking among adults with HIV, the nationally representative 2015 Youth Risk Behavior Survey (which includes data from 15,624 adolescent students in Grades 9 to 12) found that students who had ever used synthetic cannabinoids engaged in riskier activities, including sex, than students who only used marijuana.[59] While the available data suggest that the use of marijuana is not associated with

decreased adherence to ART,[60] data are lacking on the impact of synthetic cannabinoids on ART adherence. Finally, with the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these products, which may increase the risk of opioid overdose.

Management of Cannabis and Cannabinoid Use

Because of the aforementioned concerns regarding cannabinoid use, particularly the variety of compounds and neuropsychiatric effects, people with HIV should be discouraged from using cannabinoids until more data are available. No pharmacological treatment exists for cannabinoid use disorder; however, behavioral health treatment may be effective for some patients.[61-63]

Club Drugs

Epidemiology

Club drugs are recreational substances that have euphoric or hallucinogenic effects or that are used to enhance sexual experiences.[5] The use of multiple club drugs or other drugs simultaneously is common. Although these substances are used by many different people with HIV, the majority of data come from MSM with HIV. Use of club drugs in this population has been shown to negatively impact HIV treatment.[64] Club drugs include methylenedioxymethamphetamine (MDMA), GHB, ketamine, benzodiazepines (see the benzodiazepine section above), and other drugs that are used to enhance sexual experiences (e.g., mephedrone, inhaled nitrates [poppers], and phosphodiesterase-5 inhibitors [PDE5] for erectile dysfunction). Survey data from users of club drugs also have revealed that efavirenz is purchased by people without HIV for its intoxicating effects.[65]

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.[53,64,66]

Management of Club Drug Use

Treatment strategies for club drug use have not been well studied in controlled trials.[67] No recommended pharmacotherapies exist at this time, and the most common strategy for treating patients 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.[53,66] Overdoses secondary to interactions between club drugs (i.e., MDMA or GHB) and protease inhibitor–based ART have been reported.[53] For instance, using PDE5 or ketamine concurrently with potent CYP3A4 inhibitors, such as ritonavir or cobicistat, can lead to potentiation of the effects of these substances.[64]

Cocaine

See the discussion in the section on stimulants below.

Opioids

Epidemiology

Opioids remain a significant concern for people with HIV, both for the acquisition of HIV and as major contributors to morbidity and mortality. Overdose involving opioids is the leading cause of accidental death in the United States.[68] 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.[69] To combat the opioid overdose epidemic, health care providers should prescribe naloxone for opioid overdose prevention for all patients who are using opioids beyond the short-term treatment of acute pain.[3]

Risk-Taking Behaviors and the HIV Care Continuum

Many people who use opioids start by using opioid tablets (e.g., oxycodone) that are ingested orally or crushed and sniffed. Once tolerance develops, some individuals move from sniffing the crushed tablets to injecting heroin purchased on the streets. This transition from sniffing to injecting dramatically increases the risk of HIV and HCV infection.

Low-cost heroin is often a mix of heroin and higher potency synthetic opioids, such as fentanyl.[68] Methamphetamines and cocaine also have been combined with fentanyl but at a lower rate than heroin.[70,71] With the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these as well. In all instances where fentanyl or other high-potency opioids are added to other drugs, the risk of overdose increases.

Although treatment for an opioid use disorder can improve HIV treatment outcomes, it is not a prerequisite for treating HIV, as some patients are able to adhere successfully to ART despite ongoing opioid use. Although ART coverage among people with HIV who injected drugs increased from 58% to 71% between 2009 and 2015, additional work is needed to improve ART coverage in this population.[72] Data from the Johns Hopkins HIV Clinical Cohort (2001–2012) demonstrated that in the early years of the cohort, people who injected drugs were less likely to be retained in care; however, this gap in retention had closed by 2012, and people who injected drugs and noninjectors had similar probabilities of being on ART and having a suppressed viral load during the later years of the cohort.[73]

Management of Opioid Use

FDA has approved three medications for the treatment of opioid use disorder that can help decrease or eliminate opioid use, reduce the risks of morbidity and mortality that are associated with opioid use, and improve HIV treatment success. These medications, collectively termed medication-assisted treatment (MAT), include buprenorphine, methadone, and naltrexone (see Table 13 below). Buprenorphine and methadone are opioid agonists (the use of these drugs is termed opioid agonist therapy [OAT]), whereas naltrexone is an opioid-antagonist or "blocker." Both buprenorphine and naltrexone can be prescribed in the setting of routine HIV clinical care.[74] Prescribing buprenorphine requires specific training and licensure (known as an X-waiver; see the SAMHSA website for more information). Methadone must be prescribed through a licensed opioid treatment program (OTP). An OTP directory also can be found on the SAMHSA website.

Use of buprenorphine or methadone can lead to reductions in risky behaviors associated with HIV transmission, psychosocial and medical morbidity related to opioid use disorder, and criminal behaviors. People who are receiving treatment for opioid use are already engaging with the health care system; therefore, they are more likely to initiate treatment for HIV and to be adherent to their ARV regimens. Both buprenorphine and methadone are cost-effective interventions at the societal level.[75] Methadone has better retention in SUD treatment than either buprenorphine or naltrexone, and it should be considered for individuals who do not achieve successful outcomes with buprenorphine or naltrexone.[76] Buprenorphine has a lower risk of overdose than methadone. In addition, it can be prescribed in primary care offices. Patients who are taking buprenorphine have significantly better retention in treatment than those who are taking daily oral naltrexone.[77] Although several randomized, controlled clinical trials have demonstrated efficacy for naltrexone when treating opioid use disorder, subsequent study results have been disappointing; one meta-analysis revealed that oral naltrexone was equivalent to placebo.[78] To address the adherence challenges with naltrexone, a depot formulation was created for monthly administration. This preparation has the potential to improve adherence; however, studies that compare opioid agonists, such as buprenorphine and methadone, to depot naltrexone as treatments for opioid use disorder have not been conducted. In a randomized, placebo-controlled trial in people with both HIV and opioid use disorder, participants who received at least three doses of depot naltrexone before discharge from prison achieved longer periods of continuous abstinence after transitioning from prison to the community than those who received either placebo or two or less doses of depot naltrexone.[46] On the basis of these data, methadone or buprenorphine generally are used as first-line agents for the treatment of opioid use disorder. Depot naltrexone is used as an alternative treatment for people who have been released recently from correctional facilities when other options are not available.

Important pharmacokinetic interactions between these medications (particularly methadone) and certain ARV drugs are listed in Drug–Drug Interactions.

Stimulants

Epidemiology

Cocaine and methamphetamine are powerful stimulants that have been associated with multiple detrimental effects to people with HIV, including accelerated disease progression, poor ART adherence, and lack of viral suppression. Cocaine powder is snorted or injected, whereas the free-base form (crack) is smoked. Methamphetamines can be taken orally or rectally, injected, or smoked. Cocaine and methamphetamine commonly are used with other substances, including alcohol, and can be combined with fentanyl, which increases the risk of overdose.[70,71] 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.[79-81] Methamphetamine use is more common among MSM,[82] and increased rates of cocaine use have been observed among ethnic and racial minorities and persons with a history of incarceration.[83]

Risk-Taking Behaviors and the HIV Care Continuum

Multiple negative health consequences of stimulant use are observed among people with HIV, including rapid development of dependence and adverse effects on multiple organ systems,

particularly the central nervous and cardiovascular systems. Stimulant use is associated with neurocognitive impairment,[84] delirium, seizures, hemorrhagic strokes, and mental health disturbances, including anxiety, psychosis, and paranoia.

Stimulant use may lead independently 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.[85-88] Stimulant use has been associated with poor HIV continuum of care outcomes, including suboptimal rates of ART adherence, retention in care, and viral suppression. 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.[89]

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).[90,91] Among people with HIV who use crack and opioids, MAT for opioid use disorder may improve ART adherence and viral suppression.[92,93] Limited evidence indicates that some pharmacologic interventions (e.g., methylphenidate, modafinil, bupropion, naltrexone)[94] can reduce methamphetamine use or cravings. A double-blind, placebo-controlled trial of extended-release injectable naltrexone plus oral extended-release buproprion in adults with moderate or severe methamphetamine use disorder demonstrated a higher response of urine samples free of methamphetamines compared to placebo (weighted average response of 13.6% with naltrexone-buproprion and 2.5% with placebo, $P < 0.001$); however, the overall response rate was low.[95] No recommended pharmacotherapy exists to treat stimulant use disorder in people with HIV.

Several behavioral interventions have shown promise in randomized trials. People with HIV who received motivational interviewing sessions, cognitive behavioral therapy, or a combination of the two decreased their stimulant use and improved their adherence to ART, and they were less likely to engage in risky sexual behaviors.[12] Contingency management has been shown to be effective in decreasing stimulant use among people with HIV, but the sustained effects on the reduction of stimulant use and improvements in ART adherence are less clear.[13,80,96] 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.[97] People with HIV who use stimulants benefit most from multidimensional interventions that target substance use, ART adherence, and risky sexual behaviors.[12]

Despite the challenges discussed above, people with HIV who use stimulants can achieve viral suppression with ART[98] 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% versus 16.8%).[99] 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.[99]

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.[100,101] 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.[100] 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.[102-104]

Managing Tobacco Use

To maximize the survival benefits of ART, clinicians should consider using evidence-based behavioral and pharmacological[105-107] cessation strategies when treating patients with HIV who smoke tobacco (see the tools and recommendations provided by the CDC and the U.S. Preventive Services Task Force). These include (but are not limited to) advising the patient to quit smoking, using the five A's, employing motivational interviewing, and referring the patient to a tobacco quitline. Pharmacotherapies for smoking cessation (nicotine replacement therapy, bupropion, and varenicline) have few clinically significant interactions with ARV drugs and can lead to enormous reductions in morbidity and mortality if the person is able to stop smoking. Nicotine replacement is efficacious;[108] however, bupropion doubles rates of smoking cessation compared with nicotine replacement therapy.[109] Varenicline is a partial nicotine receptor agonist. In comparative studies, varenicline was more effective than bupropion in smoking cessation.[109,110] Clinical trials among people with HIV have found varenicline to be both effective and safe.[105,107] In a recent randomized controlled trial among 179 individuals with HIV who were randomized 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% versus 12.1%, OR 4.5; 95% CI, 1.83–11.2) and produced higher continuous abstinence between weeks 9 and 12 (23.6% versus 10%, OR 4.65; 95% CI, 1.71–12.67) compared to placebo.[107] Although significant between-group differences were not observed after 24 weeks, these data support the use of varenicline among people with HIV. Varenicline should be used in combination with relapse prevention strategies and other measures for long-term tobacco cessation.

Table 16. 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 patients with CrCl 30–50 mL/min	No significant interaction with ARV drugs expected.	Contraindicated in patients 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 patients regarding disulfiram reaction when taken with alcohol; symptoms for the reaction may include flushing, tachycardia, nausea, vomiting, or hypotension.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Has the greatest efficacy of all FDA-approved medications for alcohol use disorder.
Opioid Use Disorder			
Buprenorphine	Individualize buprenorphine dosing based on a patient's opioid use. The dose range is 4–24 mg sublingually. Dosing is once daily or twice daily.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug-Drug Interactions for further recommendations.	Buprenorphine has 90% first-pass hepatic metabolism. Verify that the patient is using the appropriate technique for sublingual administration before adjusting the dose, because improper administration will result in poor absorption and low drug levels.
Methadone	Individualize the dose. Patients who receive higher doses (>100 mg) are more likely to remain in treatment.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug-Drug Interactions for further recommendations.	QTc prolongation is a concern at higher doses. Methadone can be prescribed for OUD only by a licensed OTP.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Longer time of continuous abstinence in those who received depot formulation naltrexone compared with placebo after transition from prison to community.

Table 16. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction with ARV Drugs	Comments
Nicotine Use Disorder			
Nicotine Replacement Therapy	FDA has approved a wide variety of nicotine-replacement products. All formulations are effective.	No significant interaction with ARV drugs expected.	Work with the patient to identify the route of delivery that the patient 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).	Concentration may be reduced when used with ARV drugs that are CYP2D6 inducers. See Drug-Drug Interactions for further recommendations.	Tobacco quit date ideally should be 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 patients with CrCl <30 mL/min.	No significant interaction with ARV drugs expected.	Tobacco quit date ideally should be 1 week after starting therapy.

Key: ARV = antiretroviral; CrCl = creatinine clearance; CYP = cytochrome P; FDA = Food and Drug Administration; FPV = fosamprenavir; LPV/r = lopinavir/ritonavir; OUD = opioid use disorder; OTP = opioid treatment program; PO = orally; RTV = ritonavir

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Transgender People with HIV

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Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all transgender people with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners (AI). • HIV care services should be provided within a gender-affirmative care model to reduce potential barriers to ART adherence and to maximize the likelihood of achieving sustained viral suppression (AII). • Prior to ART initiation, a pregnancy test should be performed for transgender individuals of childbearing potential (AIII). • Some antiretroviral drugs may have pharmacokinetic interactions with gender-affirming hormone therapy. Clinical effects and hormone levels should be routinely monitored with appropriate titrations of estradiol, testosterone, or androgen blockers, as needed (AIII). • Gender-affirming hormone therapies are associated with hyperlipidemia, elevated cardiovascular risk, and osteopenia; therefore, clinicians should choose an ART regimen that will not increase the risk of these adverse effects (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Because transgender and nonbinary people bear a disproportionate burden of HIV, it is important for HIV care providers to be knowledgeable about the specific HIV care needs of these individuals.

Terminology

Transgender people are broadly defined as those whose gender identity differs from their assigned sex at birth.[1,2] The terminology used to define transgender identities continues to evolve over time and across geographical and cultural contexts.[3] The terms cisgender, cis-man, and cis-woman are used to describe persons who identify with their assigned sex at birth. The terms used to describe women who were assigned male at birth include transgender women, trans women, transfeminine individuals, and women of transgender experience. The terms for men who were assigned female at birth include transgender men, trans men, transmasculine individuals, and men of transgender experience. Some individuals identify outside the gender binary of man or woman, using words such as gender nonbinary, genderqueer, and gender nonconforming to describe themselves. Other individuals may not have a fixed sense of their gender and may move back and forth among different gender identities; these individuals are described as gender fluid. Agender persons do not identify with having any gender and can use other terms, such as null-gender or neutrois.

Gender affirmation describes processes whereby a person receives social recognition, value, and support for their gender identity and expression.[4] Gender affirmation is often described across several dimensions, including social (e.g., social support and acceptance, use of pronouns, names, or clothing that align with their gender identity), medical (e.g., use of hormones or surgery), legal (e.g., legal name change or changing gender markers on identity documents), and psychological (e.g., the degree

of self-acceptance and comfort with their gender identity).[5] Medical gender affirmation has been shown to improve mental health outcomes and measures of well-being in transgender individuals.[6,7]

Epidemiology

National surveys indicate that 1.4 million adults in the United States aged 18 years and older identify as transgender, representing 0.6% of the adult population.[8] It is estimated that almost 2% of high school students identify as transgender.[9,10] National, population-based estimates of the numbers of gender nonbinary people in the United States are not yet available; however, 31% of the 27,715 people who completed the 2015 U.S. Transgender Survey (USTS) identified as gender nonbinary.[11] Meta-regression modeling suggests that the number of people who are willing to report that they are transgender and/or gender nonbinary is likely to increase in the future.[12]

The most recent estimate of HIV prevalence among transgender people is 14% among transgender women and 2% among transgender men.[13] The highest prevalence is among Black (44%) and Hispanic/Latino (26%) transgender women.[13] Not enough data were available to estimate HIV prevalence by race/ethnicity among transgender men. Data on HIV prevalence among nonbinary individuals is scant. Of the nonbinary individuals who completed the 2015 USTS, 0.4% self-reported having HIV, including 1% of participants who were assigned male at birth and 0.2% of participants who were assigned female at birth.[11]

In the first national-level analysis of transgender people with HIV, the National HIV Surveillance system identified 2,351 transgender people with newly diagnosed HIV infection from 2009 to 2014. Eighty-four percent of these individuals were transgender women, 15% were transgender men, and 0.7% reported other gender identities.[14] More than one-half of both transgender women (51%) and men (58%) with newly diagnosed HIV were Black/African American. Most of these individuals were aged 25 years to 34 years (35%) or 20 years to 24 years (26%). Almost one-half of transgender people with newly diagnosed HIV resided in the South (44%), and 18% had AIDS at the time of diagnosis.

In 2017, the Ryan White HIV/AIDS Program provided services for 8,811 transgender people, representing 1.8% of Ryan White clients.[15] Of these transgender clients, 7,837 (89%) were transgender women, 853 (10%) were transgender men, and 121 (1%) were transgender with current gender unknown. The majority were Black and/or African American (5,081 individuals [57.6%]) or Hispanic/Latino (2,619 individuals [29.7%]).

HIV Care Continuum

Some studies have reported that transgender women with HIV are less likely than cisgender men to receive antiretroviral therapy (ART), be adherent to ART, and achieve viral suppression.[16-21] Transgender people may experience numerous barriers to successful engagement along the HIV care continuum.[11,22] For example, compared with Ryan White clients overall, transgender clients were significantly less likely to have stable housing (77% vs. 87%), live above the federal poverty level (24% vs. 37%), and be virally suppressed (81% vs. 86%).[15] Experiences of violence, discrimination, and other trauma[11] are common among transgender people and have been associated with ART failure.[23]

Barriers to HIV Care and Treatment

Transgender people may avoid the health care system due to stigma and past negative experiences (e.g., being called the wrong name or pronoun, being verbally harassed, asked invasive questions about being transgender, or having to educate their providers about transgender people).[11,13,14,24-26]

For many transgender people, gender-affirming therapy (e.g., feminizing hormones) is a greater priority than HIV treatment and care.[27,28]

Concerns about adverse interactions between antiretroviral (ARV) drugs and gender-affirming hormone therapy are common among transgender people.[27] One study found that 40% of transgender women with HIV did not take their ARV drugs as directed due to concerns about drug–drug interactions, yet less than half had discussed this concern with their providers.[29]

Facilitating HIV Care Engagement

Gender Affirmation

Individuals are more likely to engage in HIV care when gender affirmation needs are met.[4,25] A national study of transgender people with HIV found that participants who work with HIV care providers who affirm their gender (e.g., providers who use their chosen name and pronoun) were more likely to be virally suppressed.[28] Adherence to hormone therapy correlates with adherence to ART.[30,31] However, making access to hormone therapy contingent upon ART adherence is associated with lower likelihood of viral suppression.[28]

Integration of HIV Care with Gender Care

According to research with transgender youth[25] and adults,[27] integrating HIV care with gender care facilitates treatment and is associated with higher rates of viral suppression. In addition to minimizing the number of provider visits and potentially stressful clinical interactions, care integration makes it easier to discuss concerns about drug–drug interactions between HIV treatment and gender-affirming medications. In instances where integrated care is not feasible, the ART prescriber should refer the patient to an appropriate hormone therapy prescriber. Collaboration between these two care providers may enhance the quality of care.

Peer Navigation

Peer navigation has been found to improve the likelihood of durable viral suppression among key populations, including among transgender women.[32] Research with youth and adults suggests that having visible transgender staff in the clinical environment also facilitates engagement in care.[25]

Gender-Affirming Clinical Settings

Providing HIV services within gender-affirming environments should be a priority. Concrete steps that clinicians can take include ensuring that registration forms and electronic medical records are inclusive of transgender and gender nonbinary identities, preferably using a two-step method that records both gender and sex assigned at birth.[33] Individuals should be asked for their chosen name and pronouns, and these should be used consistently when speaking to or about the person, regardless of legal name. Clinicians and staff should avail themselves of resource lists, brochures, and other materials that meet the specific needs of transgender people with HIV.

Integrating hormone therapy with HIV services is the recommended practice; this requires HIV providers to become knowledgeable about hormone therapy and other aspects of gender-affirming services. When integration of HIV and transgender services is not possible, patients should be referred to clinicians who are knowledgeable in the field of transgender medicine. Both the World Professional Association for Transgender Health (WPATH) and GLMA: Health Professionals Advancing LGBTQ Equality (previously known as the Gay & Lesbian Medical Association) have provider directories that list endocrinologists, primary care providers, and psychiatrists with expertise working with transgender populations.

Pharmacological Considerations

Hormone Therapy

Hormone therapy is an important aspect of gender-affirming care for many transgender individuals. Hormones facilitate the acquisition of the secondary sex characteristics that are associated with the affirmed gender. Several guidelines for hormonal treatment of transgender people have been published, including guidelines from the Endocrine Society[34] and WPATH.[35] Clinical outcomes, potential adverse effects, the patient's treatment goals, and the patient's current hormone levels should be taken into account when determining the appropriate doses of hormone and androgen blockers. A clinician should be aware of the typical doses and routes of administration for all of the hormones and androgen blockers that a patient is taking, whether these medications are prescribed or not. All additional interventions (such as gonadectomy) should be documented. These interventions could potentially increase the risk of ART-related adverse effects on cardiovascular and bone health.

Feminizing regimens that are used by transgender women and others who were assigned male at birth usually include estrogens and androgen blockers. Feminizing regimens result in breast growth, redistribution of body fat, softening of the skin, and a decrease in muscle mass.[32] These regimens do not reduce facial (beard) hair or change the voice. In the United States, oral, parenteral, or transdermal preparations of 17-beta estradiol, or, less often, conjugated estrogens, are the mainstay of gender-affirming medical care for transgender women. Spironolactone, a mineralocorticoid receptor antagonist with anti-androgen properties, is usually used for androgen blockade; alternatives include 5-alpha reductase inhibitors that decrease the production of dihydrotestosterone (e.g., finasteride or dutasteride) or gonadotropin-releasing hormone agonists (e.g., goserelin acetate and leuprolide acetate). Cyproterone acetate is a steroidal anti-androgen that is frequently used outside of the United States. Patients may request progesterone to assist with breast growth; however, this has not been proven to be effective.[33] When using feminizing regimens, the goal is to suppress the testosterone level to <50 ng/dL and reach a serum estradiol level in the physiologic cisgender female range of 100 pg/mL to 200 pg/mL.[34]

Masculinizing regimens for transgender men and others who were assigned female at birth involve parenteral or transdermal testosterone preparations. These regimens are designed to stimulate the growth of facial and body hair, increase muscle mass, and deepen the voice; use of these regimens also results in clitoral enlargement, vaginal atrophy, and amenorrhea.[34] When using masculinizing therapy, the testosterone levels should be kept in the usual cisgender male range of 400 ng/dL to 700 ng/dL.[34]

Hormones and Antiretroviral Therapy

Studies that have examined interactions between exogenous estrogens and ART have predominantly focused on combined oral contraceptive use in cisgender women.[36] The data from these studies have been used to make predictions about the direction and extent of drug-drug interactions (Table 17). However, there are known differences between the pharmacologic characteristics of ethinyl estradiol, which is used in contraceptives, and 17-beta estradiol, which is used for gender affirmation. These differences may influence the accuracy of the predictions about the interactions between feminizing hormonal regimens and ART.

Table 17. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with the Least Potential to Impact GAHT Drugs	All NRTIs Entry Inhibitors • IBA • MVC • T-20 Unboosted INSTIs • BIC • DTG • RAL NNRTIs • RPV • DOR	None	No dose adjustments necessary. Titrate dose based on desired clinical effects and hormone concentrations.
ARV Drugs That May Increase Concentrations of Some GAHT Drugs	EVG/c All boosted PIs	Dutasteride Finasteride Testosterone	Monitor patient for associated adverse effects; decrease the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs That May Decrease Concentrations of GAHT Drugs	PI/r NNRTIs • EFV • ETR • NVP	Estradiol	Increase the dose of estradiol as needed to achieve the desired clinical effects and hormone concentrations.
	NNRTIs • EFV • ETR • NVP	Dutasteride Finasteride Testosterone	Increase the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.

Table 17. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with an Unclear Effect on GAHT Drugs	EVG/c PI/c	Estradiol	There is the potential for increased or decreased estradiol concentrations. Adjust the dose of estradiol to achieve the desired clinical effects and hormone concentrations.

Note: See Tables 24a, 24b, 24c, 24d, and 24e for additional information regarding drug–drug interactions between ARV drugs and gender-affirming medications.

Key: ARV = antiretroviral; BIC = bictegravir; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GAHT = gender-affirming hormone therapy; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; T-20 = enfuvirtide

Other Hormonal Therapy Considerations

Bone Health

Bone metabolism is influenced by sex hormones. Current recommendations for osteoporosis screening are based on age and sex and have not been studied in transgender populations, which include people who have used hormone therapy and/or undergone removal of their gonads. Studies investigating bone mineral density changes in transgender women have shown inconsistent results, with the use of estrogens being associated with both elevations and declines in bone mineral density.[37-39] In one study, transgender women had high rates of osteopenia even before initiating hormones, possibly due to low levels of physical activity and low vitamin D levels.[37] Transgender men who are receiving testosterone appear to maintain adequate bone mineral density.[40] The risk for osteoporosis increases after gonadectomy for both transgender men and transgender women, especially if hormone regimens are stopped. Consequently, clinicians should consider early screening in this setting.

When using the FRAX® tool, which requires a sex designation, expert consensus is that assigned birth sex should be used, since transgender people who initiate hormones in early adulthood have generally already achieved peak bone mass.[41] Transgender people with HIV should be screened for osteoporosis using dual-energy X-ray absorptiometry by age 50, in accordance with current primary care recommendations.[42]

Since the use of tenofovir disoproxil fumarate (TDF) has been associated with reductions in bone mineral density in people with HIV, TDF should be used with caution in transgender people with risk factors for osteoporosis or in those with established osteoporosis.

Interpretation of Laboratory Values

Interpretation of laboratory results requires special attention when reference ranges vary by sex. The sex listed on laboratory requisition forms typically corresponds with the gender listed on the patient's insurance forms and may not reflect the patient's current anatomical or hormonal configuration. Normal values have not been established for transgender individuals who are receiving gender-affirming hormonal or surgical interventions. Interpretation of laboratory results is dependent on the

patient's physiology and the specific test being performed. Feldman et al.[43] recommend the following:

- For transgender people who are not taking hormones and have not had gonadectomy, use the sex assigned at birth.
- For transgender people who have undergone gonadectomy and have been stable on hormone therapy, use their affirmed gender.
- For transgender people who retain natal gonads and who may have been on hormone therapy for shorter periods of time, some laboratory tests may require the use of male reference ranges, while others may require the use of female reference ranges.
- Guidelines from the Center of Excellence for Transgender Health[1] recommend using the limits of normal described in the table below.

Limits of Normal When Interpreting Selected Laboratory Results in Transgender Adults

Laboratory Measures	Transgender Women on Gender-Affirming Hormones		Transgender Men on Gender-Affirming Hormones	
	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Alkaline Phosphatase	Not defined	Male value	Not defined	Male value
Creatinine	Not defined	Male value	Not defined	Male value
Hemoglobin/Hematocrit	Female value	Male value	Male value[a]	Male value

[a] If the patient is menstruating regularly, consider using the female lower limit of normal.

Providers are encouraged to consult with their local laboratories to obtain hormone level reference ranges for both male and female norms, and then apply the correct range when interpreting results based on the current hormonal sex, rather than the sex on the laboratory form.[1] Reference intervals for transgender people have not been established; therefore, hormone status and clinical judgment must be used to assess abnormal laboratory values.[44]

Renal Concerns

Gender-affirming hormones can affect estimates of glomerular filtration rates (eGFR) that rely on serum creatinine due to changes in muscle mass. In one study, transgender men on testosterone had a mean increase in levels of serum creatinine from 0.73 ± 0.03 mg/dL to 0.87 ± 0.04 mg/dL after 3 to 6 months of treatment. Transgender women on estrogen had a decrease in mean serum creatinine levels from 0.90 ± 0.03 mg/dL to 0.85 ± 0.03 mg/dL.[45] Creatinine-based eGFR calculations may therefore overestimate GFR in transgender women on hormones or underestimate GFR in transgender men on hormones. Therefore, using cystatin C-based eGFR calculations may be preferred for patients with marginal renal function.

Cardiovascular Disease Risk

Transgender individuals may have elevated cardiovascular disease (CVD) risk, due to both traditional risk factors and the risk factors associated with hormone use. Rates of tobacco use are higher among transgender people than in the general population,[46] and transgender women have a

higher risk of venous thromboembolism and ischemic stroke, primarily associated with duration of estrogen use.[47] Transgender women on estrogens may show an increase in serum levels of triglycerides and high-density lipoproteins (HDL) and a decrease in levels of low-density lipoproteins (LDL).[48] Exogenous testosterone has been associated with increased levels of LDL and decreased levels of HDL among transgender men.[48] Providers should take CVD risk into consideration when selecting ART regimens and gender-affirming hormone therapy regimens.

Assessment of cardiac risk among transgender people with HIV can be complicated by hormone-induced changes in lipid levels as well as sex-specific variations in levels of homocysteine and high sensitivity C-reactive protein.[49] American Heart Association guidelines recommend using sex-specific calculators to determine cardiovascular risk and guide interventions,[50] and they provide no guidance for transgender people whose assigned sex at birth may differ from their hormonal and/or anatomical sex. The Center of Excellence for Transgender Health recommends that providers use the risk calculator for the sex at birth, affirmed gender, or an average of the two depending on the age at which the patient began using hormones and the total amount of time that a patient has been on hormone therapy.[1]

For transgender people with an elevated CVD risk or a history of CVD events, ARV drugs that are associated with CVD should be avoided whenever possible. See Table 20 for a list of ARV drugs that are associated with an increased risk of CVD. See Table 21 for alternative ARV agents to use in individuals with CVD. In transgender women who have an elevated risk for CVD or who have experienced a CVD event, transdermal estradiol may be the safest option for hormone therapy, because it carries a lower risk of thromboembolism than other routes of administration.[51]

Pregnancy Potential

Important information on contraception, drug–drug interactions between ARV drugs and hormone therapy drugs, and pregnancy is provided in Women with HIV. Much of this information also applies to transgender and nonbinary individuals. Below are specific ART considerations for transgender and nonbinary people of childbearing potential. Clinicians who care for pregnant patients should also consult the current Perinatal Guidelines for a more in-depth discussion and guidance on managing these patients.

Some transgender individuals use exogenous hormones and/or undergo gonadectomy for gender affirmation. Understanding exactly what interventions someone has undergone and the timeline for these interventions will clarify the patient's potential for pregnancy. Transgender individuals without a uterus (by birth or by hysterectomy) do not have pregnancy potential. Ovulation may continue in the presence of hormone therapy in transgender people with a uterus and ovaries, and these individuals may retain their fertility.[1] Gender-affirming surgeries do not impair fertility unless the uterus, ovaries, and vagina are removed.[52,53]

All transgender people who have a uterus and ovaries and engage in sexual activity that could result in pregnancy should receive a pregnancy test prior to initiating ART **(AIII).** Data from an observational study in Botswana suggest that there is an increased risk of neural tube defects (NTDs) in infants born to women who were receiving dolutegravir (DTG) at the time of conception; however, the risk of these defects was low.[54] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[55] Before initiating an integrase strand transfer inhibitor-based regimen in a person of childbearing potential, clinicians should review

Table 6 for information to consider when choosing an ART regimen. All ART-naive persons who are pregnant should be started on ART for their health and to prevent transmission of HIV to the fetus. They should be counseled about ARV drug use during pregnancy, and clinicians should consult the Perinatal Guidelines when designing a regimen **(AIII)**.

Testosterone Exposure in Transgender Persons with Ovaries

Testosterone alone is not a reliable form of contraception, and pregnancies have been reported in transgender men following prolonged testosterone treatment. Testosterone is a teratogen, and it is contraindicated in pregnancy. Clinicians should assess the reproductive desires and fertility potential of their transgender patients and provide accurate information on contraceptive and reproductive options.[56]

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Women with HIV

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Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all people with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners without HIV (AI). • When prescribing antiretroviral (ARV) drugs for women with HIV, clinicians should consider that some ARV drugs have significant pharmacokinetic (PK) interactions with hormonal contraceptives (AII) and hormone replacement therapy (BIII). Consult Tables 24a, 24b, 24d, and 24e for detailed recommendations and a summary of available data when selecting ARV and hormone combination therapy (AIII). • Clinicians should consider the possibility of weight gain in women when initiating or changing ART, because women in general and Black women in particular experience greater weight gain with ART over time than men (AI). • A pregnancy test should be performed for women of childbearing potential before initiation of ART, and the choice of ART should be guided by recommendations from the Perinatal Guidelines (AIII). • When selecting or evaluating an ARV regimen for women with HIV of childbearing potential, clinicians should consider the regimen's effectiveness, the woman's hepatitis B status, the teratogenic potential of the drugs in the ARV regimen, and the possible adverse outcomes for the mother and the fetus (AII). • During pregnancy, an additional goal of ART is to maintain a viral load below the limit of detection throughout pregnancy in order to reduce the risk of HIV transmission to the fetus and newborn (AI). • When selecting an ARV regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and PK data on the use of each agent during pregnancy. The risks and benefits of ARV use during pregnancy should be discussed with all individuals of childbearing potential (AIII), and clinicians should consult the Perinatal Guidelines when designing a regimen (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*

This section focuses on some unique clinical and therapeutic issues to consider and basic principles to follow when caring for cisgender women with HIV. Cisgender women are defined as individuals who were assigned female at birth and who identify themselves as women. In this section, cisgender women will be referred to as "women." Some topics discussed in this section—such as contraception, drug–drug interactions between antiretroviral (ARV) drugs and hormonal therapy, and pregnancy—also apply to transgender men (men assigned female at birth), and individuals assigned female at birth who identify as nonbinary (gender identities that are not exclusively feminine or masculine) or gender fluid (gender identity is not fixed). See Transgender People with HIV for more information on the specific HIV care needs of these individuals. Clinicians who care for pregnant patients should consult the Perinatal Guidelines for a more in-depth discussion on treating pregnant patients and guidance on managing these patients.

Sex Difference Considerations in Antiretroviral Therapy

In general, studies to date have not shown sex differences in virologic responses to antiretroviral therapy (ART).[1-5] However, limited data show that pharmacokinetics (PKs) for some ARV drugs may differ between men and women, possibly because of variations in factors such as body weight,

plasma volume, gastric emptying time, plasma protein levels, cytochrome P450 activity, drug transporter function, and excretion activity.[6-9]

Adverse Effects

Several studies with older ARV drugs have suggested that sex may influence the frequency, presentation, and severity of some ARV-related adverse events. Most notably, women are more likely to develop severe symptomatic hepatotoxicity with nevirapine[10,11] and lactic acidosis with prolonged use of zidovudine (ZDV), stavudine, and didanosine.[12]

Some studies have investigated how metabolic complications that are associated with the use of ARV drugs differ between women and men. At 96 weeks after initiation of ART, women with HIV were less likely to have decreases in limb fat but more likely to have decreases in bone mineral density (BMD) than men with HIV.[13,14] Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and some ARV drugs.[15-18] ARV regimens that contain tenofovir disoproxil fumarate (TDF), ritonavir-boosted protease inhibitors (PI/r), or both are associated with a significantly greater loss of BMD than regimens that contain other nucleoside reverse transcriptase inhibitors (NRTIs) and raltegravir (RAL).[19-22] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide (TAF) may be considered as alternatives to TDF for patients who are at risk of osteopenia or osteoporosis. Recommendations for the management of bone disease in people with HIV have been published.[23]

Weight Gain and Antiretroviral Therapy

Weight gain after initiation of ART, especially in people with advanced HIV, can be a sign of a return to better health. However, as discussed below, recent and emerging data from clinical trials and longitudinal cohort studies suggest sex differences in ARV-associated weight gain across all classes of ART among treatment-naive individuals, particularly with the use of certain integrase strand transfer inhibitors (INSTI)-based regimens (dolutegravir [DTG] and bictegravir [BIC]). In a pooled analysis of eight randomized controlled trials with ARV-naive people with HIV initiating treatment, at follow-up, female sex was associated with 1.5 times the odds of a ≥10% weight gain compared with male sex (17.4% vs. 12.2%), with Black females significantly more likely to experience a ≥10% weight gain than non-Black females (19.7% vs. 12.4%).[24] At 144 weeks of follow-up in the ADVANCE study, a 12.3-kg weight gain was recorded among women receiving TAF/emtricitabine (FTC)/DTG compared with 7.4 kg and 5.5 kg in TDF/FTC/DTG and TDF/FTC/efavirenz (EFV), respectively.[25] In addition to women being more likely to experience weight gain with ARV initiation, the pattern of weight gain differs between men and women. In the ADVANCE study, women gained more fat than lean body mass than men, with weight gain concentrated in the limbs and trunk at 96 weeks of follow-up. ARV-associated weight gain similarly has been observed among virologically suppressed women switching to an INSTI-based regimen.[26,27] In the Women's Interagency HIV Study, virologically suppressed women who switched to an INSTI-based ART or had an INSTI added to their regimen (n = 234) gained an average of 4.2 kg in body weight at the 2-year follow-up compared with 0.2 kg in women remaining on non-INSTI ART (n = 884).[27] Mean change in percent body fat (1.7% vs. 0.3%) and body circumference measures were also greater in the INSTI group than in the non-INSTI group. Investigators did not detect a difference in weight gain by individual INSTI.

All these data indicate that ARV-associated weight gain should be a factor to consider when initiating or changing ART, particularly in Black women. To date, it remains unclear whether

switching to a non-INSTI-based regimen results in the reversal of weight gain. It should be noted that, although randomized controlled trials and observational studies suggest that individuals receiving INSTI-based regimens experience greater weight gain than those receiving comparator regimens, significant uncertainty continues as to whether INSTIs are causing weight gain or whether the comparator drugs are suppressing weight gain. For example, a recent analysis in the ADVANCE trial demonstrated that the greater weight gain observed in DTG- versus EFV-treated participants was dependent primarily on cytochrome P450 Family 2 Subfamily B Member 6 (CYP2B6) polymorphisms associated with slow EFV metabolism (and presumably higher EFV levels). Among those with rapid EFV metabolism genotypes, no evidence was found for a difference between DTG- and EFV-treated participants.[28] The underlying mechanisms for this weight gain 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

Multiple observational studies have found that women are more likely than men to have suboptimal adherence to ART. Defining adherence as missing no dose of ART in the prior three days, the Centers for Disease Control and Prevention analyzed data from the nationally representative Medical Monitoring Project (n = 12,394) by race and gender.[29] Race comparisons by gender indicated that women had consistently lower ART adherence than men of the same race. Adherence rates were 94% for White men compared with 88% for White women; 93% for Latino men compared with 88% for Latina women; and 89% for Black men compared with 87% for Black women. A Canadian study followed 4,534 individuals (including 904 women) for a median of 65.9 months and found that a significantly lower proportion of women relative to men were optimally adherent (57.0% vs. 77.1%).[30] In the analysis adjusted for ethnicity and injection drug use, female sex remained associated independently with suboptimal adherence. Women with HIV face multifactorial barriers to adherence. However, increasing access to social services—such as food, housing, and transportation—has been associated with improved ART adherence, as have social support and good patient–provider relationships.[31,32] Another analysis of 6,186 women from the Medical Monitoring Project found that women age 50 and older were more likely to be adherent to ART than women younger than 50.[33] However, menopausal symptoms have been associated significantly with suboptimal ART adherence in cross-sectional[34] and longitudinal studies[35] of older women with HIV. It also was noted that 68.8% of older women with HIV experienced symptoms of menopause, but only 17% received treatment for these symptoms. It is plausible that treating menopausal symptoms may improve ART adherence among older women with HIV.[35]

Antiretroviral Therapy Considerations in Adults and Adolescents with HIV Who Are of Childbearing Potential

All adults and adolescents with HIV who are of childbearing potential should be offered comprehensive reproductive and sexual health counseling and care as part of routine primary medical care. Topics for discussion should include safe sex practices, reproductive desires and options for conception, the HIV status of sexual partner(s), the use of effective contraception to prevent unplanned pregnancy, and maintaining viral suppression to optimize health in preparation for pregnancy. Counseling also should include discussion of special considerations pertaining to ARV use when using hormonal contraceptives, when trying to conceive, and during pregnancy (see the Perinatal Guidelines). Clinicians should discuss intentions regarding pregnancy with all persons of childbearing potential, and a pregnancy test should be performed before initiating ART **(AIII).**

Antiretroviral Regimen Considerations for Individuals Who Are Trying to Conceive or Who Cannot Use Effective Contraception

EFV is teratogenic in nonhuman primates.[36] However, in humans, no increase in teratogenicity has been reported with the use of EFV. Based on drug-specific risk assessments by the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to EFV have been monitored with no increase in the risk of overall birth defects detected, including in cardiovascular and genitourinary systems. Individuals who become pregnant while on EFV-containing regimens should continue their current regimens **(BIII).**

Preliminary data from the birth outcomes surveillance study in Botswana raised concern of an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[37,38] Folate fortification of grains in the geographic area of this study was not mandatory and was uncommon. Folate prescribed before conception was low (0.1% to 0.2%) among the study participants.[39] Updated results from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[40] Because folic acid is known to prevent NTDs in the general population, all pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI).**

Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review the What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient section and the Perinatal Guidelines for information to consider when choosing an ARV regimen. The key recommendations are listed below:

- **For individuals who are trying to conceive**, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating one of the following regimens, which are designated as *Preferred* regimens during pregnancy in the Perinatal Guidelines: a dual NRTI-inhibitor combination (ABC plus lamivudine [3TC] or TDF plus either FTC or 3TC) and either a PI/r (atazanavir/r or darunavir [DRV]/r) or an INSTI (DTG or RAL) **(AIII).** Clinicians should discuss the risks and benefits of using DTG with patients to allow them to make an informed decision (see the Perinatal Guidelines). Compared with other ARV drugs, the advantages of DTG include once-daily dosing and better tolerability. DTG-based regimens also are associated with rapid, durable viral load suppression, which is important for maternal health and the prevention of perinatal HIV transmission. Data are insufficient to recommend BIC at this time. The use of long-acting injectable (LAI) cabotegravir (CAB) with rilpivirine (RPV) has not been studied in pregnancy and currently **is not recommended** in individuals who are trying to conceive **(AIII).**

For individuals who are not planning to conceive but who are sexually active and not using contraception, consider a regimen's effectiveness and tolerability, the available data on potential teratogenicity, and the person's preferences (e.g., pill burden) when choosing between regimens that are recommended for initial therapy (see Table 6). Clinicians should refer to the Perinatal Guidelines for recommendations.

Reproductive Options for Couples with Differing HIV Status

Couples with differing HIV status should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include screening and treating both partners for sexually transmitted infections and using ART to maximally suppress and maintain the viral load of

the partner with HIV. For couples with different HIV serostatus, 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).[41-43]

Hormonal Contraception

Safe and effective reproductive health and family planning services to prevent unplanned pregnancies and perinatal transmission of HIV are essential components of care for individuals with HIV of childbearing potential. These individuals should receive ongoing counseling on reproductive issues. Individuals who do not desire pregnancy currently but are sexually active or considering initiating sexual activities should be offered effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Individuals with HIV can use all available contraceptive methods (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs),[44] after consideration of potential drug–drug interactions as discussed in the next section (see the Perinatal Guidelines).

Drug–Drug Interactions

Interactions between ARV drugs and hormonal contraceptives may reduce contraceptive efficacy. However, most data are generated from healthy-volunteer, short-duration PK studies, and clinical data regarding interactions between ARV drugs and hormonal contraceptives in women with HIV are limited. The magnitude of change in drug concentrations that may reduce contraceptive efficacy or increase the risk of adverse effects is not known for all forms of contraceptives, making the clinical implications of some ARV-hormone drug interactions challenging to interpret.

Concerns about PK interactions between hormonal contraceptives and ARV drugs should not prevent clinicians from prescribing hormonal contraceptives for individuals on ART who prefer a contraceptive method. However, an alternative or additional effective contraceptive method is recommended when significant interactions occur between hormonal contraceptives and ARV drugs (see Tables 24a, 24b, 24d, and 24e). A summary of ARVs with known interactions with hormonal contraceptives is described below:

Combination contraceptives containing ethinyl estradiol and progestins, including combined oral contraceptives (COCs), transdermal patches, and intravaginal rings:[45,46]

- EFV significantly decreases progestin concentrations from both COCs and intravaginal rings, which may increase the risk of contraceptive failure. EFV did not reduce oral ethinyl estradiol exposure in one small study, but it did reduce exposure when combined with an intravaginal ring, which may increase the risk of intermenstrual bleeding (spotting), particularly with ultra-low and low-dose estrogen-containing contraceptives.
- Elvitegravir boosted with cobicistat (EVG/c), and cobicistat- or ritonavir-boosted PIs decrease ethinyl estradiol levels, which may increase the risk of intermenstrual bleeding (spotting), particularly with ultra-low and low-dose estrogen-containing contraceptives. However, these ARV regimens also increase progestin exposure, which preserves contraceptive effectiveness.
- Cobicistat- and ritonavir-containing regimens should be avoided with drosperinone-containing products because of an increased risk of hyperkalemia.

- Fostemsavir (FTR) increases ethinyl estradiol exposure, which may increase risk of thromboembolic events. Product labeling recommends a maximum dose of ethinyl estradiol 30 mcg per day when combined with FTR.[47]

Progestin only pills:[45,46]

- EFV significantly decreases concentrations of oral progestin pills, including emergency contraception, which may increase the risk of contraceptive failure.
- Cobicistat- or ritonavir-boosted ARV regimens may increase progestin exposure. The combination may be used without dose adjustment; monitor for progestin-related adverse effects.

Injectable Contraceptives (depot-medroxyprogesterone):

- One study of EFV-based ART plus depo-medroxyprogesterone acetate (DMPA) did not find a significant reduction in medroxyprogesterone acetate (MPA) exposure. No change in DMPA dose or frequency is necessary.[48]
- For women receiving both rifampin and EFV for the treatment of tuberculosis (TB) and HIV, some experts suggest administering DMPA every 8 to 10 weeks, instead of every 12 weeks. This recommendation is based on the results of one study of 42 women with HIV and TB in South Africa, which found 12% of participants with MPA concentrations below the level of contraceptive effectiveness at Week 12.[49] One study of EFV-based ART plus DMPA did not find a significant reduction in MPA exposure.[48]

Progestin-Releasing Contraceptive Implants:[45,46]

- EFV significantly decreases progestin concentrations released from a contraceptive implant. Cohort studies have found that women receiving EFV-based ART and contraceptive implants have a higher rate of unintended pregnancies than women receiving other ART combinations.[50,51]
- Cobicistat- or ritonavir-boosted ARV regimens may increase progestin exposure, but the combination may be used without dose adjustment.

Risk of HIV Transmission to Sexual Partner

Despite their contraceptive benefits, concerns exist that certain types of hormonal contraception may increase the risk of HIV transmission. Oral contraceptive use in people on ART does not increase the risk of HIV transmission, although the data are limited.[52] Also, no evidence indicates an increased risk of transmission with contraceptive implants.[53] However, in a prospective study from Africa, injectable contraceptives were found to be associated with a significantly increased risk of HIV-1 transmission from women (who were not on ART) to their male partners. Higher HIV-1 RNA concentrations in endocervical secretions were detected in women with HIV who were using injectable contraceptive methods than in those who were not receiving any hormonal contraceptives, offering a potential mechanism for increased HIV-1 transmission risk.[54] A World Health Organization expert group reviewed all available evidence regarding hormonal contraception use and HIV transmission to a partner without HIV and recommended that individuals with HIV can continue to use all existing hormonal contraceptive methods without restriction.[55] Further research is needed to determine definitively whether hormonal contraceptive use is an independent risk factor for transmission of HIV, particularly in the setting of ART. Regardless, the potential association between

hormonal contraception use and HIV transmission in the absence of ART underscores the importance of ART-induced viral suppression to reduce transmission risk.

IUDs appear to be a safe and effective contraceptive option for individuals with HIV.[56-58] Although studies have focused primarily on IUDs that do not contain hormones (e.g., copper IUDs), several small studies have found that levonorgestrel-releasing IUDs are also safe and are not associated with increased genital tract shedding of HIV.[59-63]

Pregnancy

All women with HIV should receive ART early in pregnancy, regardless of their viral load or CD4 T lymphocyte (CD4) cell count, for their own health and for the prevention of perinatal HIV transmission and transmission of HIV to sexual partners. ARV drugs reduce the risk of perinatal HIV transmission by decreasing maternal viral load in blood and genital secretions.[64-66] Clinicians who are caring for pregnant adults and adolescents with HIV should review the Perinatal Guidelines.

Antiretroviral Regimen Considerations

In general, the recommendations for the use of ART in pregnant women are the same as those for women who are not pregnant. As in nonpregnant individuals, genotypic drug-resistance testing is recommended for all people who are pregnant before initiating ARV drugs **(AIII)** and for those with detectable HIV RNA while on ART **(AI).** However, ART initiation should not be delayed pending genotypic drug-resistance test results. The ARV regimen can be modified, if necessary, once the resistance test results are available **(BIII).** Unique considerations that influence recommendations on the ARV drugs to use during pregnancy include the following:

- Potential ARV-associated adverse effects for pregnant women, fetuses, and infants, including potential interactions with other medications women may already be receiving;
- Need for strict adherence to the prescribed ARV regimen to avoid drug resistance, optimize health outcomes, and minimize the risk of perinatal transmission; and
- Limited long-term outcome data for infants who were exposed to ARV drugs *in utero*, especially for newer ARV drugs.

Clinicians should review the Perinatal Guidelines for ARV drug recommendations for individuals who recently have received an HIV diagnosis or those who become pregnant while on ART. Selection of ARV drugs for women who are pregnant should be individualized according to specific ARV history, the results of drug-resistance assays, and the presence of comorbidities, as well as the individual's preferences for balancing known and unknown risks and benefits of an ARV regimen. Because of data suggesting decreased drug levels during pregnancy and associated loss of virologic suppression, cobicistat-containing regimens, including EVG/c or DRV/c, are not recommended for initiation during pregnancy.[67] A pregnant woman who has a suppressed plasma viral load on one of these regimens could continue the regimen with frequent viral load monitoring (e.g., every month). Alternatively, an alternative regimen can be used for the duration of the pregnancy. The use of LAI CAB with RPV has not been studied in pregnancy. In clinical trials, participants who became pregnant were switched from LAI CAB and RPV to an alternative oral ARV regimen throughout the remainder of their pregnancies.[68] Women who become pregnant while on therapy will need close oversight and their pregnancy outcomes should be reported to the Antiretroviral Pregnancy Registry.

The registry collects observational data regarding exposure to U.S. Food and Drug Administration–approved ARV drugs during pregnancy to assess potential teratogenicity.

If maternal HIV RNA is ≥1,000 copies/mL (or unknown) near delivery, intravenous infusion of ZDV during labor is recommended, regardless of the mother's antepartum regimen and resistance profile and the mode of infant delivery **(AI).** Administration of combination ART should continue during labor and before a cesarean delivery (oral medications can be administered with sips of water during this time).

Clinicians who are treating pregnant individuals with HIV are strongly encouraged to report cases of prenatal exposure to ARV drugs (either administered alone or in combination) to the Antiretroviral Pregnancy Registry.

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for nonpregnant adults and adolescents. Maternal ART should be continued after delivery. For more information regarding postpartum management of HIV, refer to the Perinatal Guidelines.

Several studies have demonstrated that adherence to ART may decline during the postpartum period.[69-71] Clinicians should address ART adherence at each postpartum clinic visit, including an evaluation of specific factors that facilitate adherence or present 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 reversible contraceptive—such as an implant or IUD—is desired by the patient, it should be inserted before hospital discharge or during the postpartum visit.

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.[72] Evidence suggests that women with HIV are reaching menopause at earlier ages than those who do not have HIV.[73,74] However, other confounding factors may affect age of menopause in women with HIV, such as sociodemographic factors, illicit drug use, hepatitis C coinfection, smoking, and possibly ART.

A Canadian study of 229 women with HIV reported that the average age of menopause was 48 years, which was three years younger than the general Canadian population. Lower level of education and hepatitis C coinfection were associated independently with menopause at <45 years of age.[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 also 48 years of age. Age at menarche <11 years, cigarette smoking, chronic hepatitis C, and CD4 count <50 cell/mm^3 were associated significantly with an earlier age of natural menopause.[76]

Defining the relationship between HIV and menopausal symptoms, mental health, and depression is complicated due to overlapping symptoms from HIV itself, effects of ART, other comorbidities, and

substance use. Some studies suggest that women with HIV experience a greater burden of menopausal symptoms, including vasomotor symptoms, sexual dysfunction, and mood changes.[73,74,77] Other studies did not find differences between women with HIV and those without HIV.[78,79] Menopausal symptoms also have been associated with reduced adherence to ART and poor cognitive performance.[34,35,80,81]

No studies have shown evidence of estrogen deficiency (i.e., menopause) affecting CD4 count, plasma HIV viral loads, or response to ART.[82,83] Two small studies showed no difference in plasma levels of tenofovir and RAL between pre- and post-menopausal women.[84,85]

The use of hormone replacement therapy (HRT) is low among women with HIV.[35] Data are limited on drug-drug interactions between ART and estradiol as part of HRT, and drug interaction data with ethinyl estradiol cannot be extrapolated to the estrogens used for HRT because of differences in metabolism. Drug interactions between HRT and ART are possible, particularly regimens containing cobicistat, ritonavir, PIs, or some non-nucleoside reverse transfer inhibitors. See the drug–drug interaction Tables 24a, 24b, 24d, and 24e for predicted interactions and clinical recommendations.

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Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis B Virus/HIV Coinfection

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Panel's Recommendations
• Before initiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (AIII). • Because emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have activity against both HIV and HBV, an antiretroviral (ARV) regimen for patients with both HIV and HBV should include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive ARV regimen (AI). • In people with HBV/HIV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended (AII), because HBV resistance to these drugs can emerge. • If TDF or TAF cannot be safely used, the alternative recommended HBV therapy is entecavir, in addition to a fully suppressive ARV regimen (BI). Entecavir has weak activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when given to patients with HBV/HIV coinfection (AII). Peginterferon alfa monotherapy also may be considered in certain patients (CII). • Other HBV treatment regimens, including adefovir alone or in combination with 3TC or FTC and telbivudine, are not recommended for patients with HBV/HIV coinfection (CII). • Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against stopping these medications, and they should be carefully monitored during interruptions of HBV treatment (AII). • When switching "or modifying" an ARV regimen in a person with HBV/HIV coinfection, ARV drugs that are active against HBV should be continued (AII) or specific anti-HBV drugs should be initiated. • HBV reactivation has been observed in people with HBV infection during interferon-free hepatitis C virus (HCV) treatment. For that reason, all patients initiating HCV therapy should be tested for HBV. People with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Approximately 5% to 10% of people with HIV in the United States also have chronic hepatitis B virus (HBV) infection.[1] The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in people with HBV/HIV coinfection than in people with chronic HBV monoinfection.[2] Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T lymphocyte cell responses following initiation of antiretroviral therapy (ART).[3,4] However, antiretroviral (ARV) drug toxicities or several liver-associated complications attributed to flares in HBV activity after initiation or

discontinuation of dually-active ARV drugs can affect the treatment of HIV in patients with HBV/HIV coinfection.[5-7] These complications include the following:

- Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are ARVs approved to treat HIV that are also active against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV.[8]
- The anti-HBV drug entecavir has activity against HIV. However, when entecavir is used to treat HBV in patients with HBV/HIV coinfection who are not on ART, the drug may select for the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in patients with HBV/HIV coinfection, entecavir must be used in addition to a fully suppressive ARV regimen **(AII).**[9]
- When 3TC is the only active drug used to treat chronic HBV in patients with HBV/HIV coinfection, 3TC-resistant HBV emerges in approximately 40% and 90% of patients after 2 and 4 years on 3TC, respectively. Therefore, FTC, which is similar to 3TC, should be used in combination with other anti-HBV drugs **(AII).**[10]
- In patients with HBV/HIV coinfection, immune reconstitution following initiation of treatment for HIV and HBV can be associated with elevated transaminase levels, possibly because HBV-induced liver damage is primarily an immune-mediated disease.[11]
- Some ARV agents can increase liver transaminase levels. The incidence and magnitude of these increases are higher with HBV/HIV coinfection than with HIV monoinfection.[12-14] The etiology and consequences of these changes in transaminases are unclear, because the changes may resolve with continued ART. Nevertheless, some experts suspend the suspected agent(s) when the serum alanine transferase (ALT) level increases to 5 to 10 times the upper limit of normal or at a lower threshold if the patient has symptoms of hepatitis and/or new elevations in bilirubin. However, increased transaminase levels in people with HBV/HIV coinfection may indicate hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution; thus, the cause of the elevations should be investigated before discontinuing medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe, as well as HBV DNA levels, which should decrease in the setting of immune reconstitution.

Recommendations for Patients with HBV/HIV Coinfection

- All patients with chronic HBV should be evaluated to assess the severity of HBV infection (see Hepatitis B Virus in the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV). Patients with chronic HBV also should be tested for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and, if nonimmune, receive the HAV vaccination. In addition, patients with chronic HBV should be advised to abstain from alcohol and also counseled on prevention methods that protect against both HBV and HIV transmission.[15]
- Before ART is initiated, all persons who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV DNA by using a quantitative assay to determine the level of HBV replication **(AIII),** and the test should be repeated every 3 to 6 months to ensure effective HBV suppression. The goal of HBV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) is to prevent liver disease complications by sustained suppression of HBV replication. A recent

large cohort study found that persistent HBV viremia on 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.[16]

- Because HBV reactivation has been observed in people with HBV infection during interferon-free hepatitis C virus (HCV) treatment,[17,18] people with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes agents with anti-HBV activity (such as [TDF or TAF] plus [FTC or 3TC]) prior to initiating HCV therapy **(AIII).** The diagnosis of HBV reactivation should be considered in people with current HBV infection who experience elevated liver enzymes during or immediately after HCV therapy.

Antiretroviral Drugs with Dual Activities Against HBV and HIV

Among the ARV drugs, 3TC, FTC, TAF, and TDF all have activity against HBV. Entecavir is an HBV nucleoside analog that has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicities than TDF, although weight gain does occur more commonly with TAF than TDF.[19,20]

The efficacy of TDF versus TAF in patients with HBV monoinfection was evaluated in a randomized controlled trial of HBV treatment-naive and treatment-experienced HBeAg-negative patients. In this study, TAF was noninferior to TDF based on the percentage of patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = 0.47$).[21] TAF also was noninferior to TDF in HBeAg-positive patients with chronic HBV monoinfection, with a similar percentage of patients achieving HBV DNA levels <29 IU/mL at 48 weeks of therapy (64% for TAF vs. 67% for TDF; $P = 0.25$).[22] In both studies, patients on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than patients receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to 48 weeks also favored TAF.[21,22]

In patients with HBV/HIV coinfection, (TAF or TDF) plus (3TC or FTC) can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, TDF is fully active for the treatment of people with known or suspected 3TC-resistant HBV infection, whereas 3TC resistance compromises the activity of entecavir against HBV.

Recommended Therapy

The combination of (TAF or TDF) plus (3TC or FTC) should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection **(AII).**[23-25] The decision whether to use a TAF- or TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and for acceleration of bone loss, and balanced with the potential for weight gain with TAF as compared with TDF. In a switch study in patients with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ARV regimen to the fixed-dose combination elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/c/TAF/FTC) maintained or achieved HBV suppression with improved eGFR and bone turnover markers.[26] TAF/FTC-containing regimens currently approved for the treatment of HIV infection **are not recommended** for use in patients with creatinine clearance <30 mL/min (except for patients receiving hemodialysis). Although data on switching from a TDF-based to a TAF-based ARV regimen are limited, the data from the EVG/c/TAF/FTC switch study suggest that patients with HBV/HIV coinfection can switch

to TAF/FTC-containing regimens with a potential reduction in renal and bone toxicity while maintaining HBV suppression.

Alternative Therapy

If TDF or TAF cannot be safely used**,** entecavir should be used in addition to a fully suppressive ARV regimen **(AII);** however, entecavir should not be considered as part of the ARV regimen **(BII).**[27] Because entecavir and 3TC share a partially overlapping pathway to HBV resistance, it is unknown whether the combination of entecavir plus 3TC or FTC will provide greater virologic or clinical benefit than entecavir alone. In people with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (approximately every 3 months) of the HBV DNA level to detect viral breakthrough.

Peginterferon alfa monotherapy for up to 48 weeks also may be considered in some patients with HBV/HIV coinfection. However, data on the use of this therapy in people with HBV/HIV coinfection are limited and, given safety concerns, peginterferon alfa should not be used in people with HBV/HIV coinfection who have decompensated cirrhosis.

HBV Drugs Not Recommended

Other HBV treatment regimens include telbivudine used in addition to a fully suppressive ARV regimen, or adefovir used in combination with 3TC or FTC and a fully suppressive ARV regimen.[23,28,29] However, data on these regimens in people with HBV/HIV coinfection are limited. In addition, these regimens are associated with higher rates of HBV treatment failure and a higher incidence of toxicity when compared to regimens containing TDF, TAF, or entecavir. These toxicities include increased risk of renal disease with adefovir-containing regimens and increased risk of myopathy and neuropathy with telbivudine-containing regimens. Therefore, the Panel on Opportunistic Infections in Adults and Adolescents with HIV **does not recommend** adefovir or telbivudine for patients with HBV/HIV coinfection.

Changing Antiretroviral Therapy

- When switching "or modifying" an ARV regimen in a person with HBV/HIV coinfection: ARV drugs that are active against HBV should be continued **(AII)** or specific anti-HBV drugs should be initiated.
- **Need to discontinue ARV medications active against HBV in patients with HBV/HIV coinfection:** Withdrawal of HBV active treatment in a patient with active HBV infection **is not recommended** in patients with HBV/HIV coinfection. If a recommended active HBV drug cannot be continued (tenofovir, entecavir), presumably due to concern for safety, and HBV active therapy must be withdrawn, the patient's clinical course should be monitored with frequent testing of liver transaminases and total bilirubin. The risk of HBV flare in this setting is highest in patients with positive HBeAg and those with active HBV. If no anti-HBV ARV drug can be used, the use of entecavir to prevent flares can be considered, especially in patients with marginal hepatic reserve—such as those with compensated or decompensated cirrhosis.[8] Recommended HBV active drugs should be used in addition to a fully suppressive ARV regimen.

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Hepatitis C Virus/HIV Coinfection

Updated: September 21, 2022
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Panel's Recommendations
• All people with HIV should be screened for hepatitis C virus (HCV) infection (AIII). Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected (AIII). • Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most patients with HCV/HIV coinfection, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count (AI). • Initial antiretroviral (ARV) regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for people with HIV who do not have HCV infection. However, when treatment for both HIV and HCV is indicated, the ARV and HCV treatment regimens should be selected with special consideration for potential drug–drug interactions and overlapping toxicities (AIII) (see discussion in the text below and in Table 18). • All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes assessing their liver fibrosis stage to guide the duration of therapy and to predict subsequent risk of hepatocellular carcinoma and liver disease complications (AIII). • Patients with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and hepatitis B core (HBcAb; total or Immunoglobulin G). Persons who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination (AIII). • HBV reactivation has been observed in people with HBV infection during HCV treatment with direct-acting antivirals. Accordingly, before initiating HCV therapy, patients with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes two agents with anti-HBV activity (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

The treatment of hepatitis C virus (HCV) infection is rapidly evolving. Patients with HCV/HIV coinfection treated with all-oral, direct-acting antiviral (DAA) HCV regimens can achieve sustained virologic response (HCV cure) at rates comparable to those in patients with HCV mono-infection.[1-3] This section of the guidelines focuses on hepatic safety and drug–drug interaction issues related to HCV/HIV coinfection and the concomitant use of antiretroviral (ARV) agents and HCV drugs. For specific guidance on HCV treatment, clinicians should refer to the HCV Guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

Approximately one-third of patients with chronic HCV infection progress to cirrhosis at a median time of <20 years.[4,5] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[6-9] A meta-analysis found that patients with HCV/HIV coinfection had a threefold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV mono-infection.[8] The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in patients with HCV/HIV coinfection, several studies have demonstrated that the rate of disease progression continues to exceed that observed in patients

without HIV.[10,11] Whether HCV infection accelerates HIV progression, as measured by the occurrence of AIDS-related opportunistic infections (OIs) or death,[12] is unclear. With older ARV drugs, people with HIV and HCV coinfection experienced higher rates of hepatotoxicity than those seen in people with HIV but not HCV.[13,14] These higher rates have not been observed with the newer ARV agents that are currently in use.

Assessment of HCV/HIV Coinfection

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

- Patients with HCV/HIV coinfection should be counseled to avoid consuming alcohol.
- Patients with HCV/HIV coinfection also should be counseled about appropriate precautions to prevent transmission of HIV and/or HCV to others.
- Patients with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and hepatitis B core (HBcAb; total or Immunoglobulin G).
    - Patients with evidence of active HBV infection (HBsAg positive) should be further evaluated and treated with ART that includes agents with anti-HIV and anti-HBV activities **(AIII).**
    - Those who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination.
- Patients with HCV/HIV coinfection who are susceptible to hepatitis A virus (HAV) should be vaccinated against HAV.
- All patients with HCV/HIV coinfection are candidates for curative HCV treatment.

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

Initiation of ART for patients with HCV/HIV coinfection should follow the recommendations for all persons with HIV infection, considering the need for concurrent HCV treatment with oral DAA regimens, the potential for drug–drug interactions, and the individual's HBV status.

Considerations When Starting Antiretroviral Therapy

The same regimens that are recommended for initial treatment of HIV in most ART-naive persons also are recommended for patients with HCV/HIV coinfection. Special considerations for ARV selection in patients with HCV/HIV coinfection include the following:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug–drug interactions with the HCV treatment regimen (see Table 18 below).
- In patients with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, before initiating HCV therapy, patients with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes agents with anti-HBV activity (such as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide plus emtricitabine or lamivudine) **(AIII).**
- Patients with cirrhosis should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and considered for liver transplantation. Furthermore, hepatically metabolized ARV and HCV DAA drugs may be contraindicated or require dose modification in patients with Child-Pugh class B and C disease (see Appendix B, Table 11).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in patients with HCV/HIV coinfection than in those with HIV mono-infection. Individuals with HCV/HIV coinfection who have advanced liver disease (e.g., cirrhosis, end-stage liver disease) are at greatest risk for DILI.[18] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[19] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 4 to 8 weeks after initiation of ART and at least every 6 to 12 months thereafter, and more often if clinically indicated. Mild to moderate fluctuations in ALT and/or AST levels (<5 times upper limit of normal [ULN]) are typical in individuals with chronic HCV infection. In the absence of signs or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART, but they do warrant monitoring to ensure a return to baseline. Patients with significant elevations in ALT or AST levels (>5 times ULN), concomitant increase in total bilirubin, or concomitant symptoms (weakness, nausea, vomiting) should be evaluated carefully for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, alcoholic hepatitis). If these signs and symptoms do not resolve, ART should be discontinued.

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found in the HCV Guidance. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug–drug interactions when used in combination. Before starting HCV therapy, the ART regimen may need to be modified to reduce the drug–drug interaction potential. Table 18 below provides recommendations on the concomitant use of selected drugs for the treatment of HCV and HIV infection. In patients receiving ART that has been modified to accommodate HCV treatment, HIV RNA should be measured within 2 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After ART modification, initiation of an HCV DAA regimen should be delayed for ≥2 weeks. Resumption of the original ARV regimen also should be delayed until ≥2 weeks after the HCV DAA regimen is completed. The prolonged half-life of some HIV and HCV drugs poses a potential risk of drug–drug interactions if a regimen is resumed soon after ART modification or HCV treatment completion.

Table 18. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults with HIV

The recommendations in this table for concomitant use of select HIV drugs with U.S. Food and Drug Administration (FDA)–approved HCV DAA drugs are based on available PK interaction data or are predictions based on the known metabolic pathways of the agents. (Instances where PK interaction data are limited or not available are indicated in the table.) Whenever HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. Because the field of HCV therapy is rapidly evolving, readers also should refer to the latest drug product labels and the HCV Guidance for updated information.

Note: Interactions with fosamprenavir (FPV) and nelfinavir (NFV) are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV PIs.

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	Individual Drugs		Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ RTV plus Dasabuvir[a]
NRTIs								
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

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	Individual Drugs		Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ RTV plus Dasabuvir[a]
PIs								
Unboosted ATV	✓	✓	✓	✓	✖	✖	✖	✓[b]
ATV/r or ATV/c	✓ ↓ daclatasvir dose to 30 mg/day	✓	✓ 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.[d]	✓ 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.[d]	✖	✖	✖	✓[c]
DRV/r or DRV/c	✓	✓			✓ If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor for TDF-associated adverse events.[d] Consider monitoring for hepatotoxicity.[e]	✖	✖	✖
LPV/r	✓	✓			✖	✖	✖	✖
TPV/r	?	✖	✖	✖	✖	✖	✖	✖

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

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	Individual Drugs		Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ RTV plus Dasabuvir[a]
NNRTIs								
DOR	✓	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓	✓
EFV	✓ ↑ daclatasvir dose to 90 mg/day	✓		✖	✖	✖	✖	✖
ETR	✓ ↑ daclatasvir dose to 90 mg/day	✓		✖	✖	✖	✖	✖
NVP	✓ ↑ daclatasvir dose to 90 mg/day	✓		✖	✖	✖	✖	✖
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

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	Individual Drugs		Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ RTV plus Dasabuvir[a]
INSTIs								
BIC/TAF/FTC	✓	✓	✓	✓	✓	✓	✓	✓
CAB PO and IM	✓	✓	✓	✓	✓	✓	✓	✖ Potential for QT interval prolongation with higher RPV concentrations. RPV is copackaged and coadministered with CAB IM.
DTG	✓	✓	✓ If used with TDF, 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

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	Individual Drugs		Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ RTV plus Dasabuvir[a]
EVG/c/TDF/FTC	✓ ↓ daclatasvir dose to 30 mg/day	✓	✖	✓ If used with TDF, monitor for TDF-associated adverse events.	✓ If used with TDF, monitor for TDF-associated adverse events. Consider monitoring for hepatotoxicity.[e]	✓ If used with TDF, monitor for TDF-associated adverse events. Consider monitoring for hepatotoxicity.[f]	✖	✖
EVG/c/TAF/FTC	✓ ↓ daclatasvir dose to 30 mg/day	✓	✓	✓	✓ Consider monitoring for hepatotoxicity.[e]	✓ Consider monitoring for hepatotoxicity.[f]	✖	✖
RAL	✓	✓	✓	✓	✓	✓	✓	✓
CCR5 Antagonist								
MVC	✓	✓	✓	✓	✓	✓	✓	✖
Attachment Inhibitor								
FTR	✓	✓	✓	✓	✖ Use alternative HCV regimen if possible.	✓	✖ Use alternative HCV regimen if possible.	✓

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

[a] Dasabuvir must be prescribed with ombitasvir/paritaprevir/RTV.

[b] Reduce ATV dose to 300 mg and instruct the patient to take it in the morning at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.

[c] This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg without COBI or RTV. The modified ARV regimen should be taken in the morning at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.

[d] Consider using an alternative HCV treatment or ARV regimen to avoid increases in TDF exposure. If coadministration is necessary, monitor patient for TDF-associated adverse events.

[e] Voxilaprevir exposures can increase when it is coadministered with pharmacologically boosted DRV or EVG. Until more safety data in clinical settings become available, patients who are receiving voxilaprevir and pharmacologically boosted DRV or EVG should be monitored for hepatotoxicity.

[f] Glecaprevir exposures can increase when it is coadministered with EVG/c. Until more safety data in clinical settings become available, patients who are receiving glecaprevir and EVG/c should be monitored for hepatotoxicity.

Key to Symbols:

✓ = ARV agents that can be used concomitantly
✖ = ARV agents not recommended
? = Data on PK interactions with ARV drug are limited or not available
↑ = Increase
↓ = Decrease

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; CCR5 = C-C chemokine receptor type 5; COBI = cobicistat; 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; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; 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
• Selection of tuberculosis (TB)-preventive treatment for individuals with HIV and latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral (ARV) regimen as noted below. o With daily isoniazid alone for 6 or 9 months, any ARV regimen can be used (AIII). o With once-weekly isoniazid plus rifapentine for 3 months: ▪ Efavirenz (EFV) 600 mg once daily or raltegravir 400 mg twice daily (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used (AII). ▪ Dolutegravir (DTG) 50 mg once daily may be used for those in whom once-daily DTG is appropriate (BII). This 3-month regimen is not recommended for patients 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). o With once-daily isoniazid and rifapentine for 1 month: ▪ EFV 600 mg once daily (in combination with either ABC/3TC or TDF/FTC) can be used without dose adjustment (AI). o If rifampin or rifapentine is used to treat LTBI, clinicians should review Tables 24a through 24e to assess the potential for drug-drug interactions among different ARV drugs and the rifamycins (AII). • All patients with HIV and active TB who are not on antiretroviral therapy (ART) should be started on ART as described below. o 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). o **CD4 counts ≥50 cells/mm^3**: Initiate ART within 8 weeks of starting TB treatment (AI). o During pregnancy, regardless of CD4 count: Initiate ART as early as feasible for treatment of the person with HIV and to prevent HIV transmission to the infant (AIII). o With TB meningitis: When initiating ART early, patients should be closely monitored, as high rates of adverse events and deaths have been reported in a randomized trial (AI). • For patients with active TB who are receiving ART, the ARV regimen should be assessed with particular attention to potential drug-drug interactions between ARVs and TB drugs. Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), in particular, have considerable potential for drug-drug interactions. The ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 24a through 24e 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 23% 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 TB infection, 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

Randomized controlled clinical trials have demonstrated that treatment with isoniazid for 6 or 9 months for latent tuberculosis infection (LTBI) in people with HIV reduces the risk of active TB, especially in those with a positive tuberculin skin test.[3] 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
- 4 months of daily rifampin
- 3 months of daily isoniazid plus rifampin

The World Health Organization (WHO)[4] and the Adult and Adolescent Opportunistic Infection Guidelines Panel (the Panel) also recommend 1 month of daily isoniazid with rifapentine as an alternative short-course regimen.

Isoniazid given daily or twice weekly for 6 or 9 months remains an alternative option, especially for patients in whom rifamycin antibiotics cannot be used.

For more than 30 years, isoniazid has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadministered with any antiretroviral (ARV) regimen. A recent study of 6,000 patients that compared completion rates, safety, and effectiveness of 4 months of rifampin versus 9 months of isoniazid found that rifampin for 4 months was non-inferior to isoniazid for 9 months for the prevention of TB disease, and that safety and completion rates were superior for 4 months of rifampin.[5] However, this trial included only 242 (4%) participants with HIV.

In the PREVENT TB study, the combination of isoniazid and rifapentine administered once a week for 3 months, as directly observed therapy, was as safe and effective as 9 months of isoniazid in preventing TB in patients with HIV who were not on antiretroviral therapy (ART).[6] Another study randomized 1,148 South African adults with HIV 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.[7]

Similarly, in 3,000 people with HIV infection in the BRIEF TB study, no difference was observed in TB incidence between those who received 1 month of isoniazid and rifapentine and those who received 9 months of isoniazid.[8] Approximately 50% of the participants were on ART while receiving the 1-month regimen; all received efavirenz (EFV)- or nevirapine-based regimens. Fewer adverse events and a higher treatment completion rate occurred with 1 month of isoniazid plus rifapentine than with 9 months of isoniazid.

Although rifapentine induces cytochrome P450 (CYP) isoenzymes and can potentially cause significant drug-drug interactions, pharmacokinetic (PK) data support its use daily or once weekly 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 IC_{90}, and all HIV viral loads remained suppressed.

The Panel recommends DTG 50 mg once daily with 3 months of isoniazid and rifapentine in patients with virologic suppression and for whom once-daily DTG is appropriate **(BII).** More importantly, this 3-month regimen **is not recommended** for patients 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.

Rifampin for 4 months also may be considered for TB-preventive treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 24a through 24e).

For pregnant women, a randomized trial of isoniazid preventive therapy (IPT) that compared isoniazid initiated during pregnancy (immediate IPT) to isoniazid delayed until 12 weeks postpartum (deferred IPT) in 956 women with HIV on ART demonstrated a greater number of adverse pregnancy outcomes in women on immediate IPT.[13] Treatment-related maternal adverse events were higher than expected in both arms, suggesting that IPT should be delayed until after delivery. However, two observational studies from South Africa showed better pregnancy outcomes and no increase in hepatotoxicity in pregnant women on ART receiving antenatal IPT.[14,15] IPT for pregnant women with HIV infection is still recommended by the WHO.[16]

If a patient with HIV is in contact with an individual 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.

Impact of Antiretroviral Therapy in Preventing Active Tuberculosis

Accumulating evidence suggests that 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 [17] 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.[18] 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 ART deferred until their CD4 count dropped to 350 cells/mm^3, or until 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.[19] Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with high prevalence of TB/HIV coinfection.

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

All patients 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 patients with active TB disease include the following:

- When to start ART in the setting of drug-resistant TB and in patients with TB meningitis,

- Significant PK drug-drug interactions between anti-TB and ARV agents, 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 patients with HIV should follow the general principles guiding treatment for patients without HIV. The Adult and Adolescent Opportunistic Infection Guidelines include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV. In general, standard anti-TB therapy should be used for patients with HIV and drug-susceptible TB, consisting of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (intensive phase), followed by 4 months of isoniazid and rifampin (continuation phase).

The TB Trials Consortium Study 31/ACTG A5349 recently demonstrated success with a shorter, 4-month regimen.[20] 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. One 4-month regimen replaced rifampin with rifapentine (rifapentine regimen). The other 4-month regimen replaced rifampin with rifapentine and ethambutol, with moxifloxacin continued throughout treatment (rifapentine-moxifloxacin regimen). In 2,516 participants, including 193 (8%) with HIV coinfection, 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 EFV-based ART or initiating EFV-based ART. In both groups, EFV concentrations were decreased slightly, but most maintained EFV concentrations of >1 mg/L and undetectable viremia.

Tuberculosis Diagnosed While a Patient Is Receiving Antiretroviral Therapy

ART should be continued when TB is diagnosed in a patient receiving ART, but the ARV regimen should be assessed with particular attention to potential drug interactions between ARVs and TB drugs (discussed below). The patient's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 24a through 24e for dosing recommendations).

Tuberculosis Diagnosed in a Patient 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.[21] The timing of ART in specific patient populations is discussed below.

Patients with CD4 Counts <50 cells/mm^3: Three large randomized clinical trials in patients 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.[22-24] In these studies, early ART was defined as starting ART within 2 weeks of and no later than 4 weeks after initiation of TB therapy.

Collectively these three trials support the initiation of ART within the first 2 weeks of TB treatment in patients with CD4 counts <50 cells/mm^3 **(AI).**

Patients with CD4 Counts ≥50 cells/mm^3: In the three studies mentioned above,[22-24] no survival benefit was seen for patients with CD4 counts ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8 to 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 patients with TB and CD4 counts ≥50 cells/mm^3.

However, given the growing body of evidence supporting early ART in general and lack of data showing any harm in patients with TB coinfection, the Panel recommends ART initiation within 8 weeks of starting TB treatment for patients with CD4 counts ≥50 cells/mm^3 **(AI).**

Patients with Drug-Resistant TB: Multidrug-resistant TB (MDR-TB) is defined as strains with resistance to both isoniazid and rifampicin; and pre-extensively drug-resistant (XDR) TB is defined as MDR-TB plus resistant to any fluoroquinolone, and XDR-TB as MDR-TB plus resistant to any fluoroquinolone and at least one additional Group A drug listed in the WHO guidelines.[25] Historically, mortality rates in patients with MDR or XDR-TB and HIV have been high,[26] but more recent data suggest that treatment outcomes are similar for patients 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 and XDR-TB, 51% of the 109 participants were living with HIV. Rates of cure, serious adverse events, and mortality were similar among those with and without HIV infection.[27]

Although randomized clinical trial data to guide the optimal timing for ART initiation are lacking, the WHO recommends ART for all patients with HIV and drug-resistant TB, irrespective of CD4 cell count, as early as possible (within the first 8 weeks), following the initiation of TB treatment.

Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged **(AIII).**

Patients with TB Meningitis: TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, patients 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 patients who received immediate ART than in those who received deferred ART (80.3% vs. 69.1% for immediate and deferred ART, respectively; $P = 0.04$).[28]

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).**

Managing patients with HIV and TB meningitis is complex, and expert consultation is encouraged **(BIII).**

Pregnant Patients: All pregnant individuals with HIV and active TB should be started on ART as early as feasible, both for treatment of the person with HIV and to prevent 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 sterilizing ability. However, they are associated with a considerable potential for drug interactions. Rifampin is a potent inducer of the hepatic CYP (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 enzymes. Rifabutin and rifapentine are CYP3A4 substrates and inducers. As potent enzyme inducers, the rifamycin antibiotics can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected include all protease inhibitors (PIs), non-nucleoside transcriptase inhibitors (NNRTIs), the INSTIs, the CCR5 antagonist maraviroc (MVC), and the gp-120-attachment inhibitor fostemsavir. Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs), the fusion inhibitor enfuvirtide, and the CD4 post-attachment inhibitor ibalizumab are not expected to have significant drug interactions with the rifamycins. Tables 24a through 24e outline the magnitude of these interactions and provide dosing recommendations when rifamycin antibiotics and selected ARV drugs are used concomitantly.

Because tenofovir alafenamide (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.[29] However, in a healthy volunteer study, following administration of TAF/emtricitabine with rifampin, intracellular tenofovir-DP concentrations were still 4.2-fold higher than those achieved by tenofovir disoproxil fumarate.[30] A clinical trial in people with HIV and TB with concomitant use of TAF and rifampin is ongoing.[31]

Several ARV drugs are not recommended for use with rifampin; clinicians should refer to Tables 24a through 24e before prescribing these drugs in combination. When DTG, RAL, or MVC are used with rifampin for TB treatment, the ARV doses must be increased. The Phase 3 REFLATE TB2 trial compared ARV regimens, including standard dose RAL 400 mg twice daily or EFV 600 mg once daily, for the treatment of HIV/TB coinfection. At Week 48, the standard dose RAL 400 mg twice-daily regimen did not demonstrate non-inferiority to EFV 600 mg once daily.[32] In contrast to its effect on other ARV drugs, rifampin leads to only modest reduction in EFV concentrations.[33,34] Even though the current EFV label recommends increasing the EFV dose from 600 mg once daily to 800 mg once daily in patients weighing >50 kg,[35] this dosage increase is generally not necessary. A reduced dose of EFV 400 mg once daily is approved for HIV treatment. Coadministration of EFV 400 mg with rifampin and isoniazid led to only limited changes in EFV area under the concentration-time curve (AUC) (<25%) in a study with 26 participants with HIV infection, and plasma concentrations were considered adequate to maintain virologic suppression.[36] Until more clinical trial data are available regarding the safety and efficacy of EFV 400 mg, the Panel continues to recommend EFV 600 mg for individuals receiving rifampin therapy.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin for TB treatment, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 24a through 24e for dosing recommendations).

Rifapentine is a long-acting rifamycin which, when given daily, is a more potent inducer than rifampin.[37] Once-daily rifapentine did not affect the oral clearance of EFV 600 mg in individuals with HIV in the BRIEF TB study,[38] and once-weekly rifapentine has 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 healthy volunteer study of DTG and weekly rifapentine with isoniazid was stopped early, following the development of an influenza-like syndrome and elevated aminotransferase levels in two of the first four participants after the third rifapentine-isoniazid dose.[39] A subsequent PK study conducted in South Africa found the combination 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 rifapentine-isoniazid dose.[12]

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome (IRIS)

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 patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.[40, 41] The syndrome 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.[42] 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 care and adherence to both antiretroviral therapy (ART) and clinic appointments should be regularly assessed. • An individual's barriers to adherence to ART and appointments should be assessed before or shortly after the initiation of ART and regularly thereafter. • 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 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 patient preferences also need to be considered. • Adherence to ART should be regularly assessed by self-report at every clinic visit. • 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 Linking patients to resources to assist with unmet social and economic needs, such as transportation, food, housing, and support services o Linking patients to counseling to overcome stigma, substance use, or depression • Multidisciplinary approaches to finding solutions to problems of adherence to ART and appointments are often necessary, including collaborations with nursing, pharmacy, social work, and case management (to the extent available). The clinician's role is to help the patient 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 the patient to resources to overcome other barriers. • Single-tablet regimens are generally recommended when clinically appropriate, but high-quality evidence to definitively recommend them is lacking, and shared decision-making with patients is essential (BIII). • At this time, evidence does not support the use of financial incentives to engage patients 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, if these methods are used, it should be in a collaborative manner to avoid promoting an adversarial relationship between the provider and patient. • The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends against the use of long-acting ART in people who have detectable viral load due to suboptimal adherence to ART and in people who have ongoing challenges with retention in HIV care, except in a clinical trial (AIII). • A summary of best practice interventions to improve linkage, retention, and adherence can be found at 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 HIV has not yet been diagnosed in about 13% of the people with HIV in the United States. Based on 2019 data, about 81% of individuals are linked to care within 30 days after receiving an HIV diagnosis. However, only 58% of people with diagnosed HIV are retained in HIV care. It is estimated that only approximately 66% of people with diagnosed HIV are virally suppressed due to poor adherence to the continuum of care and to ART.[4,5] The data for adolescents and young adults aged 13 to 14 years are even more sobering: only 51% of youth with HIV receive a diagnosis, 79% are linked to care within 1 month, and 59% are retained in care. 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.[4] 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.[6] It is also important to realize that retention and adherence are not static states. Life events, changes in insurance status, comorbid conditions, and health system changes can cause people 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.[7-9] The patient–provider relationship is central to improving patient engagement and adherence to treatment. Providers must recognize that adherence is a collaborative effort between patients and their providers.

This section provides guidance on linking patients 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. In addition, a number of other groups and organizations have provided guidance for improving adherence to the steps in the care continuum.[6,10]

Linkage to Care

Receiving a diagnosis of HIV infection 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).[11-15] In the United States, youth, people who use injection drugs, and Black/African American persons have lower rates of linkage to care.[4] Some health system factors have also been associated with linkage success or failure. Co-location of testing and treatment services[14] and active linkage services (e.g., assisting the patient in setting up appointments, maintaining an active relationship with the patient until linkage is completed, providing linkage case management services)[16-18] 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 diagnosis of HIV infection is defined as completing an outpatient appointment with a clinical provider who has the skills and ability to treat HIV infection, including prescribing ART. Patients should be linked to care as soon as possible after diagnosis with HIV, preferably within 30 days. Monitoring linkage is a critical responsibility so 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 a patient makes contact with the treating clinical system, he or she should be engaged in linkage efforts and monitored 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.[16] 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.[17] ARTAS is a strength-based intervention that aims to facilitate linkage to and retention in care for people with recently diagnosed HIV. The ARTAS intervention was tested in four cities and enrolled a diverse group of people. The participants in the ARTAS intervention trial were randomized to either an intervention arm or a control arm. Participants randomized to the control arm received information about HIV and care resources and a referral to a local HIV medical provider. Each participant 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 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 [RR] = 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 RR = 1.41, $P = 0.006$). The results from the ARTAS intervention have been replicated in a community-based study.[18] 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 living with HIV,[19] peer support,[20] and engaging with the patient at the clinic in advance of the visit with the provider.[21] Financial incentives did not increase linkage to care within 90 days in a large randomized trial.[22]

Retention in Care

Poor retention in HIV care is associated with greater risk of death.[23,24] 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.[25-28] At the provider and health system level, low trust in providers and a poor patient–provider relationship have been associated with lower retention, as has lower satisfaction with the clinic experience.[29-31] Availability of appointments and timeliness of appointments (i.e., long delay

from the request for an appointment to the appointment's date) and scheduling convenience are also factors.

Monitoring Retention in Care

Retention in care should be routinely monitored.[6] 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.[32] Both approaches are valid and independently predict survival.[33] Missed visits and a prolonged time since the last visit are relatively easy to measure and should trigger efforts to retain or re-engage 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. Intervention relied on personal contact by an interventionist with at-risk patients. It included a brief face-to-face meeting upon returning to care and at each subsequent clinic visit, plus three types of phone calls: to check on patients 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 in people with detectable plasma HIV RNA.[34] In-clinic opioid replacement therapy helps opioid users remain in care.[35] An intervention using the electronic medical record to alert providers when patients had suboptimal follow-up or high viral loads also improved retention in care.[36]

Telehealth has emerged as an important modality to see and retain patients during the COVID-19 pandemic. A cluster-randomized study conducted in the 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.[37] Reengaging and retaining people who are out-of-care remains particularly challenging. Patient navigation for out-of-care people with HIV in a New York City Medicaid health plan resulted in faster re-linkage to care but not improved retention in care.[38] In two randomized trials involving out-of-care, hospitalized patients with HIV, peer counselors and patient navigators did not improve re-linkage to care after hospital discharge.[39,40] In the only U.S.-based randomized study to test a "data to care" approach, which uses clinic and public health data to reach and reengage out-of-care people with HIV, the intervention did not result in significantly faster time to re-linkage or viral suppression.[41]

Data from nonrandomized studies are less conclusive, but there are many interventions that bear mentioning. Clinic-wide marketing (e.g., posters, brochures) and customer service training of patient-facing staff to promote attending scheduled visits and provide patients a welcoming and courteous experience have improved retention.[42] New patients who rated higher their experience with their doctor were more likely to stay in care.[43] Stepped case management and social and outreach services,[44] 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. "Data to care" approaches have helped in some jurisdictions while yielding mixed results in others,[45-47] and they require substantial resources, and privacy concerns also must be adequately addressed. As noted above, a "data to care" approach did not improve outcomes in a

randomized controlled trial. Differentiated care approaches reduce the need for appointments and other expectations for patients doing well and allow extra resources to be devoted to patients not doing well. 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 suggest the approach has beneficial impact.[48]

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 patient care experience, constructively affirming attendance rather than criticizing nonattendance, and collaboratively solving problems with patients to overcome barriers to care.[30,34,42] Flexible appointment schedules, expanded clinic hours, and copay and other financial or insurance assistance—such as that provided by the Ryan White HIV/AIDS Program—will also provide patients with uninterrupted access to clinical care. Patient navigation, telehealth, and engaging with patients 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 patients 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 4% at financial incentive clinics, from a baseline of 62%.[22] 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 withdrawal of the incentives without a persistent effect on viral suppression.[49] In another large, randomized study of persons out of care and hospitalized, financial incentives plus patient navigation did not lead to sustained improvement in retention or viral load suppression over that achieved with standard care.[39] Data are not strong enough to support the routine use of financial incentives, and they, therefore, remain experimental for use in routine care at this time.

Adherence to Antiretroviral Therapy

Adherence to ART can be influenced by a number of factors, including the patient's social situation and clinical condition, the prescribed regimen, and the patient–provider relationship.[50] 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 including trauma, 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).[51-54]

Characteristics of one or more components of the prescribed regimen can affect adherence. Once-daily regimens,[55] including those with low pill burden (even if not one pill once daily), without a food requirement, and few side effects or toxicities, are associated with higher levels of adherence.[56,57] 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 switch studies, in which persons on an MTR are randomized to stay on an MTR or switch to an STR.[58] Whether an STR is beneficial in people with HIV who are ART-naive is not

known, with observational cohort studies showing benefit of a once-daily STR versus a once-daily MTR.[57,59-62] On the other hand, observational data from Spain showed that coformulated dolutegravir/abacavir/lamivudine (DTG/ABC/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.[63] 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 with patients 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 patients' complex needs, including their medication adherence-related needs. Treatment programs for substance use may offer services that promote adherence, such as directly observed therapy (DOT).

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 patient with stable access to ART is most likely the result of poor adherence. Patient self-report, the most frequently used method for evaluating medication adherence, remains a useful tool. Carefully assessed patient self-report of high-level adherence to ART has been associated with favorable viral load responses.[64-66] Patient admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self-report 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 patients to disclose lapses in adherence, some experts suggest inquiring about the number of missed doses during a defined time period. For example, for a patient 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 patients to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale[67,68] or using qualitative response categories.[66]

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 by patients, are labor intensive, and can be perceived as confrontational, they are generally not used in routine care. Other methods of assessing adherence include the use of therapeutic drug monitoring and electronic measurement devices. However, these methods 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.[69] Some of these are commercially available, but none have been shown in randomized studies to improve outcomes. However, if these methods are used, it should be in a collaborative manner to avoid promoting an adversarial relationship between the provider and patient.

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.[65,70-72] 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 have been found to be 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.

It is important that each new patient receives and understands 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. Patients must also be positively motivated to initiate therapy, which can be assessed by simply asking patients if they want to start treatment for HIV infection. Clinicians should assist patients 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 the patient. Much of this effort to inform, motivate, and reduce barriers can be achieved by nonphysician members of the multidisciplinary team and can be accomplished concomitant with, or even after, starting therapy.[73-76] While delaying the initiation of ART is rarely indicated, some patients may not be comfortable starting treatment. Patients 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.[73-76] 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.[77,78] 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.[79] For more details, see Initiation of Antiretroviral Therapy.

Successful treatment requires a regimen that the patient can adhere to.[80,81] It is important to consider the patient's daily schedule; tolerance of pill number, size, and frequency; and any issues affecting absorption (e.g., use of acid-reducing 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, if clinically appropriate. With the patient's input, a medication choice and administration schedule should be tailored to their daily activities. Clinicians should explain to patients 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 taking can also be enhanced using medication reminder aids. The evidence is strongest for text messaging, but pill box monitors, pill boxes, and alarms may also improve adherence.[82-86]

Positive reinforcement can greatly help patients maintain high levels of adherence. This technique to foster adherence includes informing patients of their low or suppressed viral load and increases in CD4 T lymphocyte cell counts. Motivational interviewing has also been used with some success.[87-89] 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.[90] Problem-solving approaches that vary in intensity and culturally tailored approaches also are promising.[89,91,92] To maintain high levels of adherence in some patients, it is important to provide therapy for substance use and mental health and to strengthen social support. DOT has been effective in providing ART to active drug users[93] but not to patients in a general clinic population[94] or in home-based settings with partners responsible for DOT.[95,96] The use of incentives or rewards to promote adherence has been studied, and they have been shown to improve adherence in one study conducted by the HIV Prevention Trials Network (HPTN)[22] and reduce viral load in another study that required very frequent viral load measurement and incentives.[97] 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 effect after 9 months.[49] Data are too limited to support the use of financial rewards for adherence in routine care.[39,98,99]

Long-Acting Antiretroviral Therapy

A long-acting ART (LA-ART) regimen (intramuscular cabotegravir and rilpivirine) has been studied and approved for use in populations with viral suppression. There are no data on the safety and efficacy of using LA-ART in people who currently do not have suppressed HIV replication. The long pharmacologic tail of LA-ART after last dose raises concerns for the emergence of resistant mutations in people who discontinue therapy without rapidly transitioning to an oral therapy. The Panel on Antiretroviral Guidelines for Adults and Adolescents, therefore, **recommends against** the use of LA-ART in people who have detectable viral load due to suboptimal adherence to ART and in people who have ongoing challenges with retention in HIV care except in the context of a clinical trial **(AIII).**

Conclusion

Clinicians can and must obtain relatively accurate information about a patient's adherence and barriers to ART and appointment adherence, and then engage patients in a productive conversation rather than simply telling patients to be adherent and offering warnings about what might ensue with continued poor adherence. The latter approach fails to acknowledge a patient's barriers to adherence, fails to provide the patient with actionable information, erodes rather than builds the patient–provider relationship, and has been demonstrated to not improve adherence.[100,101] 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 a patient who is 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 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 access to clinicians, or linking patients to counseling to overcome stigma, substance use, or depression.
- Place patients with apparent ART adherence problems on regimens with high genetic barriers to resistance, such as DTG, bictegravir, or boosted-darunavir regimens. When selecting the regimen, consider possible side effects, out-of-pocket costs, convenience, and patient preferences, because the only regimen that will work is the one the patient can obtain and is willing and able to take.
- Understand that multidisciplinary approaches and time to understand and address barriers are needed in many situations, and that the clinician's role is to help the patient to understand the importance of adherence to the continuum of care and identify any barriers to adherence, address those that are within their immediate purview, and link the patient to resources to overcome other barriers.

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 patient-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 the patient's knowledge about HIV infection, prevention, and treatment and, based on this assessment, provide HIV-related information.	• Keeping the patient's 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 importance of staying in HIV care.
Identify facilitators, potential barriers to adherence, and necessary medication management skills both when starting ART and on an ongoing basis.	• Assess the patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges, including depression, mental illnesses, trauma, levels of social support, levels of alcohol consumption and current 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 (ADAPs), Pharmaceutical Company HIV Patient Assistance Programs and Cost-Sharing Assistance Programs). • Assist patients during insurance enrollment periods to facilitate enrollment in plans that cover antiretrovirals. • Provide resources about stable housing, social support, transportation assistance, and 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 the patient 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 regimen to predictable and routine daily events. • Consider preferential use of PI/r-based or DTG-based or BIC-based ART if poor adherence is anticipated. • Consider use of STR or fixed-dose-combination formulations to reduce pill burden. • Consider use of long-acting injectables in people with suppressed viral load if clinically appropriate. • 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 biologic 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 patients of benefits of low or nondetectable levels of HIV viral load (e.g., "Undetectable = Untransmittable") and increases in CD4 cell counts. • Thank patients for attending their appointments.
Identify the type of and reasons for poor adherence and target ways to improve 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. • The patient is unaware of appointments, or appointments are not scheduled with proper patient input. • Cost-related issues (e.g., copays for medications or visits, missed work time). • Depression, 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 patient prescription assistance programs (see above in the table, under "Provide needed resources"). • Use motivational interviews. • Provide outreach for patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Recognize positive clinical outcomes resulting from better adherence. • Arrange for DOT for persons in substance use treatment (if feasible). • Enhance clinic support and structures to promote linkage and retention (e.g., reminder calls, flexible scheduling, open access, active referrals, improved patient 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; DTG = dolutegravir; PI/r = ritonavir-boosted protease inhibitor; STR = single-tablet regimen

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Adverse Effects of Antiretroviral Agents

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Adverse effects have been reported with all antiretroviral (ARV) drugs and were among the most common reasons for switching or discontinuing therapy, and for medication nonadherence in the earlier era of combination antiretroviral therapy (ART).[1] Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events. However, the long-term complications of ART can be underestimated because most clinical trials use highly specific inclusion criteria which exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short. As ART is recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy must be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects, including diabetes and other metabolic complications, atherosclerotic cardiovascular disease, kidney dysfunction, bone loss, and weight gain. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and managed. When selecting an ARV regimen, clinicians must consider potential adverse effects, as well as the individual's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications, such as:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of adverse effects. For example, underlying liver disease from alcohol use, coinfection with viral hepatitis, and/or liver steatosis[2,3] may increase the risk of hepatotoxicity when efavirenz (EFV) or protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).
- Certain ARVs may exacerbate pre-existing conditions, for example, psychiatric disorders may be exacerbated by EFV, rilpivirine, and, infrequently, by integrase strand transfer inhibitors.[4,5]
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications, for example, when pharmacokinetic boosters such as ritonavir or cobicistat are used, or when isoniazid is used with EFV.[6]
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,[7,8] EFV neuropsychiatric toxicity,[6,9] QTc prolongation,[10,11] and atazanavir (ATV)-associated hyperbilirubinemia.[12]

Information on the adverse effects of ARVs is outlined in several tables in these Guidelines. Table 17 provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 3, 4, 5, 6, 7, 8, 9, and 10.

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy

Adverse effects for ARV drugs that are no longer commonly used in clinical practice (ddI, d4T, FPV/r, IDV, NFV, SQV/r, and TPV/r) have been removed from this table, with the exception of lipodystrophy and peripheral neuropathy associated with ddI and d4T. Because these effects may persist long after discontinuation of ddI or d4T, and patients may still present with these long-lasting toxicities, the drugs remain listed among the ARVs associated with these two effects. Refer to the product labels or to the July 10, 2019, version of the guidelines (found in the archived guidelines section of AIDS*info*) for information regarding the adverse effects associated with these older ARVs.

This table focuses on ARV-associated adverse effects that a patient may experience as a result of taking an ARV regimen. For information regarding potential adverse effects of ARVs on fetuses and newborns when certain ARVs are taken around the time of conception or during pregnancy, refer to the Perinatal Guidelines.

In this table, N/A indicates either that there are no reported cases for that particular side effect or that data for that specific ARV drug class are not available. See Appendix B, Tables 3, 4, 5, 6, 7, 8, 9, and 10 for additional information listed by drug.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Bone Density Effects	TDF: Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. TAF: Associated with smaller declines in BMD than those seen with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	ZDV: Anemia, neutropenia.	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A.	RPV, EFV: QTc prolongation.	ATV/r and LPV/r: PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	N/A	FTR: QTc prolongation was seen at 4 times the recommended dose. Use with caution in patients with pre-existing heart disease or QTc prolongation, or concomitant use of medications that may prolong QTc interval.

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Cardiovascular Disease	ABC: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	Boosted DRV and LPV/r: Associated with cardiovascular events in some cohorts	N/A	N/A
Cholelithiasis	N/A	N/A	ATV: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A
Dyslipidemia	ZDV > ABC: ↑ TG and ↑ LDL TAF: ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	EFV: ↑ TG, ↑ LDL, ↑ HDL	All RTV- or COBI-boosted PIs: ↑ TG, ↑ LDL, ↑ HDL LPV/r > DRV/r and ATV/r: ↑ TG	EVG/c: ↑ TG, ↑ LDL, ↑ HDL	N/A
Gastrointestinal Effects	ZDV > other NRTIs: Nausea and vomiting	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) LPV/r > DRV/r and ATV/r: Diarrhea	EVG/c: Nausea and diarrhea	N/A
Hepatic Effects	When TAF, TDF, 3TC, and FTC are withdrawn in patients with HBV/HIV coinfection or when HBV resistance develops: Patients with HBV/HIV coinfection may develop severe hepatic flares. ZDV: Steatosis	EFV: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3.	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported ATV: Jaundice due to indirect hyperbilirubinemia	DTG: Persons with HBV or HCV coinfection may be at higher risk of DTG-associated hepatotoxicity.	MVC: Hepatotoxicity with or without rash or HSRs reported. FTR: Transaminase elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin observed in clinical trials.

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
		NVP should never be used for post-exposure prophylaxis. EFV and NVP are not recommended in patients with hepatic insufficiency (Child-Pugh class B or C).			
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	ABC: Contraindicated if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks. HSR symptoms (in order of descending frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	NVP: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: HSR reported as part of a syndrome related to hepatotoxicity.
Injection Site Reaction		RPV IM injection: Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.		CAB IM injection: Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.	T-20 SQ injection: Reported in almost all patients; pain, tenderness, nodules, induration, ecchymosis, erythema.
Lactic Acidosis	Reported with older NRTIs, d4T, ZDV, and ddI, but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Lipodystrophy	Lipoatrophy: Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, TAF or TDF.	Lipohypertrophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/Elevated Creatine Phosphokinase	ZDV: Myopathy	N/A	N/A	RAL and DTG: ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A
Nervous System/Psychiatric Effects	History of exposure to ddI, ddC, or d4T: Peripheral neuropathy (can be irreversible).	Neuropsychiatric events: EFV > RPV, DOR, ETR. EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors. RPV: Depression, suicidality, sleep disturbances. DOR: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm.	N/A	All INSTIs: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	FTC: Hyperpigmentation.	All NNRTIs.	ATV, DRV, and LPV/r.	All INSTIs.	MVC, IBA, FTR

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Renal Effects/ Urolithiasis	TDF: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. TAF: Less impact on renal biomarkers and lower rates of proteinuria than TDF.	RPV: Inhibits Cr secretion without reducing renal glomerular function.	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. ATV: Stone or crystal formation. Adequate hydration may reduce risk. COBI (as a boosting agent for DRV or ATV): Inhibits Cr secretion without reducing renal glomerular function.	DTG, COBI (as a boosting agent for EVG), and BIC: Inhibits Cr secretion without reducing renal glomerular function	IBA: SCr abnormalities ≥Grade 3 reported in 10% of trial participants. FTR: SCr > 1.8 x ULN seen in 19% in a clinical trial, but primarily with underlying renal disease or other drugs known to affect creatinine.
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV.	Some reported cases for DRV, LPV/r, and ATV.	RAL.	N/A.
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF, and greater with DOR than EFV.			INSTI > other ARV drug classes.	N/A.

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQ = subcutaneous; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ULN = upper limit of normal; ZDV = zidovudine

Switching Antiretroviral Drugs Due to Adverse Effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis with ATV or renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching a patient from an effective ARV agent or regimen to a new agent or regimen must be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that drug resistant viruses previously acquired or selected, even those not detected by past genotypic resistance testing, are archived in HIV reservoirs. The resistant virus, even if absent from subsequent resistance test results, may reappear under selective drug pressure. See Optimizing Antiretroviral Therapy section for further discussion. It is critical that providers review the following information before implementing any treatment switch:

- The patient's medical and complete ARV history, including prior virologic responses to ART,
- All previous drug resistance test results,
- Viral tropism (if maraviroc [MVC] is being considered),
- HLA-B*5701 status (if ABC is being considered),
- Comorbidities,
- The patient's pregnancy status, ability to use effective contraceptives, and desire for pregnancy,
- Hepatitis B virus (HBV) status. Patients with evidence of chronic HBV infection should not discontinue ARVs active against HBV (e.g., TDF, tenofovir alafenamide, lamivudine, emtricitabine). If discontinuation is necessary due to adverse effects, consult the HBV/HIV Coinfection section for guidance,
- Adherence history,
- Prior intolerances to any ARVs, and
- Concomitant medications and supplements, considering any potential drug interactions with ARVs.

A patient's willingness to accept new food requirements or dosing schedule must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of comorbidities, adverse effects of concomitant medications, or HIV itself may mimic adverse effects caused by ART. Therefore, clinicians should investigate all potential causes for an adverse event. In the case of a severe adverse event, it may be necessary to discontinue or switch

ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient's HIV viral load should also be monitored to assure continued viral suppression.

Table 21 lists several major ART-associated adverse events and the options for appropriate switches between agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in an effective ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment.

Table 21. Antiretroviral Therapy–Associated Adverse Effects That Can Be Managed with Substitution of Alternative Antiretroviral Agents

This table focuses on ARV-associated adverse effects that patients may experience as a result of a current ARV regimen. For information regarding ARV choices to use in individuals of childbearing potential and during pregnancy to avoid potential ARV adverse effects on fetuses and newborns refer to the Perinatal Guidelines.

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	TAF or ABC[b] NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered, if appropriate.	Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.
Bone Marrow Suppression	ZDV	Regimen not including ZDV	ZDV has been associated with neutropenia and macrocytic anemia.
Calculi Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	This switch should be made if ATV is the presumed cause of the calculi.
Cardiac QTc Interval Prolongation	EFV, RPV, FTR	Boosted ATV or DRV, DOR, or INSTI-based regimen (that does not combine with RPV)	High EFV, RPV, and FTR exposures may cause QT prolongation. Consider switching from EFV- or RPV- based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes. For FTR, if there is no alternative ARV drug option, consider switching the concomitant medication.

Table 21. Antiretroviral Therapy–Associated Adverse Effects That Can Be Managed with Substitution of Alternative Antiretroviral Agents

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Cardiovascular Events Myocardial infarction, ischemic stroke	ABC	TDF or TAF	ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.
	RTV- or COBI-boosted PI regimens, EFV	INSTI, RPV, or DOR	If lipids are a concern, see Dyslipidemia below. Large observation cohorts have found an association between some PIs (DRV, FPV, IDV, LPV/r) and an increased risk of CV events. However, this association has not been seen with ATV. Further study is needed.
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted PI, EFV-based regimens	INSTI, DOR, or RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	Boosted ATV or DRV, INSTI, NNRTI	GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient and do not warrant ARV substitution unless they are persistent and intolerable.
	Other RTV- or COBI-boosted regimens	BIC, DTG, RAL, or NNRTI	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC.
Hypersensitivity Reaction	ABC	Any appropriate ABC-sparing regimen	Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.
	EFV, ETR, NVP, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 counts.
	DTG, RAL	Non-INSTI ART	Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases.
	MVC	Suitable alternative ART	
Insulin Resistance	LPV/r	INSTI, NNRTI	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r on insulin resistance. However, traditional risk factors for insulin resistance may be stronger risk factors than the use of any PI.
Jaundice and Icterus	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.
Lipoatrophy	Peripheral lipoatrophy (loss of subcutaneous fat of the limbs, face, and buttocks) is associated with prior thymidine analog (d4T and ZDV) use. Despite switching from these ARVs, fat recovery remains slow (may take years) and incomplete.		
Lipohypertrophy	Accumulation of visceral, truncal, dorsocervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse lipohypertrophy.		

Table 21. Antiretroviral Therapy–Associated Adverse Effects That Can Be Managed with Substitution of Alternative Antiretroviral Agents

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression, ataxia, encephalopathy	EFV, RPV	DOR, ETR, PI/c, or PI/r INSTIs may be used, but monitoring is recommended (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug, but in some patients, ataxia or encephalopathy may appear months to years after EFV-initiation. Persistent or intolerable effects should prompt substitution of EFV. INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen	Mild rashes that develop after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.
	DRV/c, DRV/r	ATV/c, ATV/r, or another drug class (e.g., INSTI)	Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.
Renal Effects Including proximal renal tubulopathy and elevated creatinine	TDF[a]	ABC,[b] TAF (for patients with CrCl >30 mL/min, unless on chronic hemodialysis), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate.	TDF may cause tubulopathy. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting.
	ATV/c, ATV/r, LPV/r	BIC, DTG, EVG/c/TAF/FTC, RAL, boosted DRV, or NNRTI	COBI, DTG, BIC, and, to a lesser extent, RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient for renal dysfunction if SCr increases by >0.4 mg/dL.

[a] In patients with chronic active HBV infection, another agent that is active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c =atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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Cost Considerations and Antiretroviral Therapy

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The clinical benefits, public health impact, and cost-effectiveness of HIV treatment have been well established since the advent of combination antiretroviral therapy (ART),[1-6] and the expanded use of ART is one of the four pillars of the *Ending the HIV Epidemic in the U.S.* initiative.[7,8] However, HIV treatment with ART is costly. A 2015 study using 2012 health care expenditure data estimated that the discounted lifetime medical costs for an individual who acquires HIV at 35 years of age is $326,500 ($597,300 undiscounted), with 60% of the costs attributable to ART.[9] The estimated total direct expenditure for HIV/AIDS care and treatment between 2002 and 2011 was $10.7 billion annually, which is 800% to 900% higher than similar expenditures for other chronic conditions.[10] These guidelines first included an antiretroviral (ARV) cost table in 2012,[11] and since then, the overall cost of brand-name, first-line ARV regimens has increased by more than 30% from 2012 to 2018,[12] which is 3.5 times the rate of inflation for that same time period. Total annual undiscounted spending on ARV drugs has more than doubled since 2010, reaching $22.5 billion in 2018.[13,14] Consequently, ART was among the top five therapeutic classes in nondiscounted spending on medications in 2018, after medications for diabetes, autoimmune diseases, cancer, and respiratory disorders.[14]

This section provides guidance on cost considerations related to HIV clinical care. The cost of ART, especially out-of-pocket costs to the patient, should be one of the many considerations in regimen selection, because such expenditures may directly affect adherence. Overall costs to the health care system, to insurers, and to society are also important, especially given the increasing number of people with HIV, rising drug costs, and increasing multimorbidity among people aging with HIV. Providers should make every effort to prevent cost from limiting HIV care.

Cost Sharing in the United States

Prescription drug pricing in the United States involves complex systems with varying requirements for mandatory and voluntary discounts, rebates, and reimbursement rates, and much of the pricing information is confidential. Prices can vary depending on the state, purchaser, type of public or private insurance coverage in use, and number of generic competitors to branded drugs (see Table 22b below). Additionally, provider-administered drugs and biologics, including those used in the management of HIV (e.g., intramuscular injections of long-acting cabotegravir [CAB] and rilpirivine [RPV]), are typically associated with product, administration, and/or office visit costs. Providers may, therefore, find it difficult to navigate payer cost-containment practices, including formulary restrictions, prior authorization requirements, and patient cost-sharing arrangements, such as copayments (a fixed dollar amount per prescription), coinsurance (a fixed percentage of the prescription cost), and insurance deductible payments.

Out-of-pocket costs for patients can be prohibitive, creating a barrier to the initiation and continuation of ART. Cost sharing results in higher rates of patients not initiating ART, prescription abandonment at the pharmacy, decreased adherence, and more frequent drug discontinuation. In turn, these may lead to worse health outcomes and an increased use of the medical system, especially among patients with chronic diseases.[15-20] Conversely, reducing patient out-of-pocket costs (e.g., through manufacturer copayment-assistance programs or by prescribing generic drugs instead of more costly brand-name products) has been associated with improved adherence.[21] Given the clear

association between out-of-pocket costs and the ability to pay for and adhere to medications, clinicians should minimize patients' out-of-pocket drug-related expenses whenever possible. However, many of the cost-sharing arrangements that determine out-of-pocket costs are not transparent to clinicians or patients at the time decisions on ART are made.

Maximum allowable copayments on prescription drugs covered by Medicaid can vary by family income, but they are usually nominal. For commercial insurers, cost sharing generally is subject to maximum payment rules under the Affordable Care Act (ACA). Manufacturer cost-sharing assistance programs are available for most brand-name ARV products but may be restricted by pharmacy and by state. Manufacturer copay assistance also may be subject to copay accumulator programs implemented by insurers' pharmacy benefit managers, whereby manufacturer payments do not count toward a patient's deductible or out-of-pocket maximum.

Medicare Part D plan cost sharing can include deductibles and copayments or coinsurance, including out-of-pocket payments of up to 25% on prescription drugs, until total out-of-pocket spending reaches $6,550.[22-24] Medicare Part B cost sharing on provider-administered drugs, such as long-acting injectable CAB and RPV or ibalizumab-uiyk (IBA) infusions, can be up to 20% of all medication costs.[25] Low-income beneficiaries may qualify for subsidies to defray Part D cost-sharing payments or the Qualified Medicare Beneficiary program to defray Part B cost-sharing payments. Manufacturer copay assistance programs may not be applied toward Medicare plan cost sharing, but assistance from independent foundations (e.g., Patient Access Network Foundation, Patient Advocate Foundation) may provide cost-sharing support if financial eligibility criteria are met.

AIDS Drug Assistance Programs (ADAPs), through the Ryan White HIV/AIDS Program (RWHAP), make ARVs and other prescription drugs accessible to people with HIV who are underinsured and have limited financial resources. Furthermore, many ADAPs provide premium and cost-sharing assistance to eligible clients covered by Medicaid, commercial insurance plans, or Medicare.[26]

Generic Antiretrovirals and Multi-Tablet Regimens

In 2017, savings to the U.S. health care system generated from the use of generic drugs and biosimilar products totaled $265 billion, including $40.6 billion and $82.7 billion in savings to Medicaid and Medicare, respectively.[27]

With substantial improvements in the long-term safety and effectiveness of contemporary ART, a number of regimens and regimen components in Table 6 remain listed beyond their patent protection date and are or will be available as lower-cost generic options. In one study, the savings associated with a transition to a hypothetical lower-cost generic ART could potentially help cover the 20-year, $480 billion projected costs to reach national treatment targets.[5]

Some research informs the cost impact of using specific generic ARV regimens or regimen components. In a cost-effectiveness analysis conducted before the availability of integrase strand transfer inhibitors (INSTIs), the use of generic efavirenz (EFV) had an estimated saving of nearly $1 billion, and a regimen with generic EFV was very cost-effective.[2] A more recent study describes a 25% reduction in both the wholesale acquisition cost (WAC) and federal supply schedule cost associated with switching from branded coformulated dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) to branded DTG plus generic ABC and generic 3TC.[2,28]

A number of generic options of ARV regimen components included in Table 6 are commercially available. Generic tenofovir disoproxil fumarate (TDF), generic 3TC, or a lower-cost, brand-name coformulation of TDF and 3TC may be combined with DTG, darunavir, or other ARVs. Generic versions of ABC, 3TC, and ABC/3TC also can be used. Generic versions of EFV, atazanavir, and ritonavir are available for use, along with lower-cost, brand-name coformulations of EFV (either 600 mg or 400 mg) with TDF and 3TC. TDF and 3TC also have been coformulated with doravirine, with a list price that is moderately lower than other single-tablet regimens (STRs) containing only proprietary ARVs (see Table 22b below).

There is keen interest in assessing the economic value of using newer, more expensive drugs compared with older, less expensive drugs that have established clinical safety and efficacy. One study investigated the cost-effectiveness of TDF-based versus tenofovir alafenamide (TAF)-based regimens.[22] The study demonstrated that the similar efficacy—but slightly improved toxicity profile—of the TAF-based regimens would justify a $1,000 higher annual premium for the TAF-based regimens. The study further highlighted that once generic TDF becomes available at much lower costs, TAF-based regimens will remain cost-effective only if their annual cost is no more than $1,000 above that of generically available TDF-based regimens. (Generic TDF was approved in 2018.)

The use of DTG plus generic 3TC for initial therapy has been evaluated in a cost-containment analysis. One study projected that if just 50% of patients 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 a 5-year period.[29] If 25% of patients with sustained viral suppression switched to branded DTG plus generic 3TC maintenance therapy, cost savings were projected to exceed $3 billion in just 5 years.[29]

Because all commercially available STRs, including those containing ARV components that are no longer patent protected, are branded products, use of generics in the United States may necessitate modest increases in pill burden, but without changes in drug frequency. One study of Medicare Part D spending, which included expenditures for one ARV fixed-dose combination tablet (ABC/3TC), demonstrated that splitting up brand-name coformulated products into their generic components could have saved Medicare an estimated $2.7 billion from 2011 through 2016, and it highlighted this approach as a critical cost-containment measure.[30] 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.[17,18] 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, particularly based on virologic outcomes and especially following viral suppression, remain limited. One large observational cohort study demonstrated a small but statistically significant virologic efficacy benefit associated with STRs.[31] In this study, the time to treatment discontinuation was shorter for non-STRs than for STR once-daily regimens; however, this difference disappeared when modifications for regimen simplification were included in the analysis. On the other hand, observational data from Spain showed that coformulated DTG/ABC/3TC resulted in similar viral suppression compared to DTG plus ABC/3TC, both when used as an initial ARV regimen and when persons with viral suppression on STR were switched to the two-pill formulation as a cost-saving strategy.[32]

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.

Costs and Cost-effectiveness of ARV Regimens for Highly Treatment-Experienced People with Multidrug-Resistant HIV

For people with multidrug-resistant (MDR) HIV, an ARV regimen that includes intravenous IBA 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.[33,34]

Laboratory Services

In the context of lifelong ART, the amount of money to be saved by performing infrequent or one-time tests (e.g., genotypes, serologies) is modest, even for expensive tests. Even so, judicious use of laboratory testing, without compromising patient care, can still be an important way to reduce costs. For patients with deductibles for laboratory tests, decreasing the use of tests with limited clinical value could reduce patient costs and improve adherence to a care plan. Several studies have examined the value of laboratory services in HIV care. One cost analysis study suggested that there may be no clinical benefit to continuing CD4 T lymphocyte (CD4) monitoring in patients with suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[19] In the United States, reducing biannual CD4 monitoring to annual monitoring could save approximately $10 million per year.[35] Another study reviewed the records of 429 hospitalizations for 274 patients with HIV during a 6-month period. The inpatient chart review demonstrated that 45% of ordered laboratory tests were not indicated, including hepatitis serologies, other serologies, and cytomegalovirus polymerase chain reaction. During this 6-month period at this single site, the estimated cost of excess and inappropriate laboratory testing totaled $14,000 to $92,000.[36]

Cost-effectiveness analyses from 2001 and 2005 demonstrated the value of genotypic resistance testing in ART-experienced and ART-naive patients and supported the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommendation to perform resistance testing before ART initiation and at time of virologic failure.[37,38] More recent cost-effectiveness analyses have revisited the value of baseline, pre-treatment genotype testing in the setting of INSTI plus two-nucleoside reverse transcriptase inhibitor (NRTI) regimens. One modeling study suggested that INSTI-specific genotype testing before initiation of a DTG plus two-NRTI regimen was not cost-effective and may lead to underutilization of INSTIs; the results highlighted that some patients with minor INSTI resistance mutations would still become virologically suppressed on a DTG-based regimen.[39] A second modeling study found that standard (NRTI, non-nucleoside reverse transcriptase inhibitor, protease inhibitor) genotype testing before ART initiation also was not cost-effective, because it may have little impact on outcomes given the use of an INSTI plus two NRTIs in first-line

treatment.[40] Both these modeling studies assessed the use of genotype testing only for decision-making for initial ART and presumed that such testing would be available for use at the time of first-line failure. The results of these modeling studies suggest that additional clinical research is needed to define the role of genotypic resistance testing before initiation of an INSTI plus 2-NRTI regimen. Importantly, these modeling data do not apply to the initiation of two-drug ARV regimens (i.e., DTG plus 3TC) or to people who have received 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 patients, with additional genotypic resistance testing for integrase mutations for individuals with a history of CAB use for PrEP (see Drug-Resistance Testing).

Costs and Cost-effectiveness of Comprehensive HIV Care

Comprehensive patient-centered HIV care offers substantial clinical benefits.[41] Such programs include integration of social service needs and services for mental health, substance use disorders, sexual health, and age-associated multimorbidity (see Substance Use Disorders and HIV, Transgender People with HIV, Adherence to the Continuum of Care, and HIV and the Older Person). Integrated services can improve engagement in care and virologic suppression among people with HIV, but they require investment and resources. Several cost-effectiveness analyses have demonstrated that integrated care programs can offer excellent value, especially if delivered to people at increased risk of disengagement in care.[42-44]

Health care access in the United States can be inequitable and limited, depending on location and income. Although the ACA has substantially improved access to HIV clinical services in many regions of the United States since 2010, an estimated 36% of people with HIV in the United States live in the 11 states that had not expanded Medicaid in accordance with the ACA as of August 2020.[26]

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.[26] 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.[45] However, because RWHAP is focused on HIV care and support services, people with HIV who have other important outpatient and inpatient health needs may experience underdiagnosis and undertreatment if patients cannot pay the out-of-pocket costs of clinical care.

Comprehensive HIV care and treatment often requires navigating a complex, dynamic patchwork of service delivery and 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 patient outcomes.

Conclusion

Ideally, costs should not drive clinical care, yet they are a factor in contemporary health care. Because regimen costs may affect patients' 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 Table 22b below for estimates of average drug prices), out-of-pocket expenditure requirements, and available generic ARV options. Providers should work with patients and their pharmacists, social workers, case managers, and peer navigators to understand their patients' medication benefits and any potential financial barriers to prescription fulfillment and full adherence. This information will help providers identify treatment options that are safe, effective, and affordable. Engaging with patients about cost constraints during the process of regimen selection will likely facilitate adherence. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company assistance programs for patients who qualify) and refer patients to such assistance if needed. Similarly, providers should help patients find comprehensive clinical care coverage when available and consider opportunities to integrate care when feasible.

Table 22a. Insurance and Health Program Prescription Drug Pricing and Access

Insurance/Health Program	Prescription Drug Pricing and Access
Medicaid	Drug manufacturers must participate in the MDRP for their drugs to be covered by Medicaid and under Medicare Part B. Manufacturers are required to pay Medicaid programs a rebate of at least 23.1% of the AMP for most brand-name drugs (13% for generics) sold to retail pharmacies or outpatient care providers (notably infused, injected, implanted, inhaled, or instilled drugs). Manufacturers pay additional rebates if this confidential AMP increases faster than the CPI-U rate of inflation. Additionally, many states negotiate with manufacturers for supplemental rebates. States are permitted to require "nominal" cost sharing for medical and pharmacy benefits for some beneficiaries, although many elect not to do so. States can obtain a waiver to allow them to apply higher cost sharing.
Medicare	ARVs are one of six "protected drug classes" under Medicare Part D. Part D plans must provide access to all, or substantially all, FDA-approved ARVs. Part-D plan sponsors, or PBMs on their behalf, negotiate rebates on outpatient drugs with manufacturers; the extent of rebating is unclear. Most physician-administered drugs and biologics are covered under Medicare Part B at a set cost: ASP plus 6%. This pricing mechanism controls spending by narrowing the spread between what is actually paid for the drug and what is actually billed to Medicare. Premiums and cost-sharing payments may be significant for both services and prescription drugs; 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.

Table 22a. Insurance and Health Program Prescription Drug Pricing and Access

	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.
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 Department of Veterans Affairs (VA), Department of Defense, Public Health Service (including the Indian Health Service), and the Coast Guard. The FCP of a drug includes a 24% discount on a drug's average price paid by non-federal purchasers. Additional discounts may be applied if non-federal purchase prices increase faster than the CPI-U inflation rate. Big Four prices may be 40% to 50% below list prices. The VA may negotiate further price reductions. Prescription drug cost sharing is generally nominal; medications are not withheld from those who cannot afford cost-sharing expenses.
Community Health Centers	Many community health centers are enrolled in the 340B Drug Pricing Program, which allows discounted drug purchasing using the MDRP formula. Discounts start at 23.1% off AMP, with additional discounts if the AMP increases faster than the CPI-U rate of inflation. Cost sharing in community health centers is first driven by payer source. For clients who are uninsured, cost sharing, if required, is typically based on a sliding fee scale.

Key: ACA = Affordable Care Act; ADAP = AIDS Drug Assistance Program; AMP = average manufacturer price; ARV = antiretroviral; ASP = average sales price; CPI-U = consumer price index-urban; FCP = federal ceiling price; FDA = U.S. Food and Drug Administration; MDRP = Medicaid Drug Rebate Program; PBM = pharmacy benefits manager

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

Table 22b includes three benchmark prices, rounded to the nearest dollar, for commonly used ARV drugs[a] as a general reference for health care providers when considering the cost of HIV treatment. Health care providers should contact patients' pharmacies or payers regarding actual prices, comparative cost savings, formulary restrictions, and patient cost-sharing requirements. **WAC** is the list price published by manufacturers for prescription drugs or biologics sold to wholesalers. The WAC price approximates what retail pharmacies pay wholesalers for single-source (e.g., brand-name) drugs. There is a range of WAC prices for generic ARV drugs, because these are multiple-source products with variable list prices. With increasing competition, actual transactional prices of generic drugs decrease substantially among wholesalers and pharmacies. **AWP** has historically been used as the basis for setting public (e.g., Medicaid) and private (e.g., commercial insurer) reimbursement rates for pharmacies. Neither WAC nor AWP includes variable price concessions along supply and payment chains, including discounts and rebates to wholesalers, pharmacies, federal purchasers (e.g., the Department of Veterans Affairs), pharmacy benefit managers, commercial insurers, Medicaid, 340B pharmacies, and ADAPs. The availability of these discounts and rebates depends on product demand, market competition, and WAC price increases set by manufacturers. Maximum Medicaid payment rates are assigned to generic products with three or more therapeutically and pharmaceutically equivalent products, as determined by the U.S. Food and Drug Administration. This federally established pharmacy reimbursement limit is the **FUL**. Federal Medicaid will reimburse state Medicaid programs up to this limit for multiple-source drugs (plus the dispensing fee); states may set their own **SMACs** and commercial insurers set their own reimbursement upper limits with pharmacies. Whereas WACs and AWPs are generally set annually, FULs are adjusted on a monthly basis, particularly for multiple-source drugs with fluctuating pharmacy acquisition costs. In this table, the FUL for a drug is described as "pending" if a generic drug currently lacks the competition required to trigger a FUL.

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Apr. 1, 2022)[c]
NRTIs					
Abacavir					
• Generic	300-mg tablet	60 tablets	$100 to $150	$578 to $603	$52
• Ziagen	300-mg tablet	60 tablets	$559	$670	
Emtricitabine					
• Generic	200-mg capsule	30 capsules	$464	$579	Pending
• Emtriva	200-mg capsule	30 capsules	$537	$644	

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

Lamivudine					
• Generic	300-mg tablet	30 tablets	$75 to $343	$324 to $430	$39
• Epivir	300-mg tablet	30 tablets	$416	$499	
Tenofovir Disoproxil Fumarate					
• Generic	300-mg tablet	30 tablets	$27 to $142	$167 to $1,216	$53
• Viread	300-mg tablet	30 tablets	$1,254	$1,504	
Zidovudine					
• Generic	300-mg tablet	60 tablets	$36 to $54	$54 to $365	$13
NRTI Combination Products					
Abacavir/Lamivudine					
• Generic	600-mg/300-mg tablet	30 tablets	$185 to $1,116	$1,393 to $1,395	$138
• Epzicom	600-mg/300-mg tablet	30 tablets	$1,292	$1,550	
Tenofovir Alafenamide/Emtricitabine					
• Descovy	25-mg/200-mg tablet	30 tablets	$2,039	$2,447	N/A
Tenofovir Disoproxil Fumarate/Emtricitabine					
• Generic	300-mg/200-mg tablet	30 tablets	$25 to $853	$70 to $2,100	$28
• Truvada	300-mg/200-mg tablet	30 tablets	$1,842	$2,211	
Tenofovir Disoproxil Fumarate/Lamivudine					
• Cimduo	300-mg/300-mg tablet	30 tablets	$1,055	$1,266	N/A
Zidovudine/Lamivudine					
• Generic	300-mg/150-mg tablet	60 tablets	$125 to $578	$265 to $932	$40
• Combivir	300-mg/150-mg tablet	60 tablets	$901	$1,082	
Abacavir Sulfate/Zidovudine/Lamivudine					
• Trizivir	300-mg/300-mg/150-mg tablet	60 tablets	$1,610	$1,932	N/A
NNRTIs					
Efavirenz					

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

• Generic	600-mg tablet	30 tablets	$80 to $980	$1,073 to $1,117	$193
• Sustiva	600-mg tablet	30 tablets	$981	$1,177	
Doravirine					
• Pifeltro	100-mg tablet	30 tablets	$1,597	$1,917	N/A
Etravirine					
• Generic	200-mg tablet	60 tablets	$1,287	$1,609	Pending
• Intelence	200-mg tablet	60 tablets	$1,439	$1,728	
Nevirapine					
• Generic	200-mg tablet	60 tablets	$10 to $45	$648 to $651	$47
• Generic XR	400-mg tablet	30 tablets	$135 to $565	$595 to $706	$149
• Viramune XR	400-mg tablet	30 tablets	$840	$1,008	
Rilpivirine					
• Edurant	25-mg tablet	30 tablets	$1,286	$1,543	N/A
PIs					
Atazanavir					
• Generic	200-mg capsule	60 capsules	$178 to $800	$1,517 to $1,668	$711
• Reyataz	200-mg capsule	60 capsules	$1,463	$1,756	
• Generic	300-mg capsule	30 capsules	$178 to $1,018	$1,502 to $1,652	$270
• Reyataz	300-mg capsule	30 capsules	$1,449	$1,739	
Atazanavir/Cobicistat					
• Evotaz	300-mg/150-mg tablet	30 tablets	$1,605	$1,927	N/A
Darunavir					
• Prezista	600-mg tablet	60 tablets	$1,948	$2,338	N/A
• Prezista	800-mg tablet	30 tablets	$1,948	$2,338	N/A
• Prezista	100-mg/mL suspension	200 mL	$1,948	$2,338	N/A
Darunavir/Cobicistat					
• Prezcobix	800-mg/150-mg tablet	30 tablets	$2,227	$2,673	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

Lopinavir/Ritonavir					
• Generic	200-mg/50-mg tablet	120 tablets	$885	$1,106	Pending
• Kaletra	200-mg/50-mg tablet	120 tablets	$1,024	$1,229	
Tipranavir					
• Aptivus	250-mg capsule	120 capsules	$1,918	$2,302	N/A
INSTIs					
Dolutegravir					
• Tivicay	50-mg tablet	30 tablets	$2,011	$2,414	N/A
• Tivicay	50-mg tablet	60 tablets	$4,022	$4,828	N/A
Raltegravir					
• Isentress	400-mg tablet	60 tablets	$1,821	$2,186	N/A
• Isentress HD	600-mg tablet	60 tablets	$1,821	$2,186	N/A
Fusion Inhibitor					
Enfuvirtide					
• Fuzeon	90-mg injection kit	60 doses (1 kit)	$3,586	$4,303	N/A
CCR5 Antagonist					
Maraviroc					
• Selzentry	150-mg tablet	60 tablets	$1,633	$1,960	N/A
• Selzentry	300-mg tablet	60 tablets	$1,633	$1,960	N/A
• Selzentry	300-mg tablet	120 tablets	$3,366	$3,920	N/A
CD4-Directed Post-Attachment Inhibitor					
Ibalizumab-uiyk					
• Trogarzo	200-mg vial	8 vials	$10,704	$12,845	N/A
gp120-Directed Attachment Inhibitor					
Fostemsavir					
• Rukobia	600-mg tablet	60 tablets	$8,027	$9,633	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

Coformulated Combination Products as Single-Tablet Regimens					
Bictegravir/Tenofovir Alafenamide/Emtricitabine					
• Biktarvy	50-mg/25-mg/200-mg tablet	30 tablets	$3,584	$4,301	N/A
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Symtuza	800-mg/150-mg/10-mg/200-mg tablet	30 tablets	$4,292	$5,151	N/A
Dolutegravir/Abacavir/Lamivudine					
• Triumeq	50-mg/600-mg/300-mg tablet	30 tablets	$3,339	$4,007	N/A
Dolutegravir/Lamivudine					
• Dovato	50-mg/300-mg tablet	30 tablets	$2,652	$3,183	N/A
Dolutegravir/Rilpivirine					
• Juluca	50-mg/25-mg tablet	30 tablets	$3,129	$3,755	N/A
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine					
• Delstrigo	100-mg/300-mg/300-mg tablet	30 tablets	$2,431	$2,917	N/A
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Generic	600-mg/300-mg/200-mg tablet	30 tablets	$120 to $252	$302 to $3,414	$144
• Atripla	600-mg/300-mg/200-mg tablet	30 tablets	$2,995	$3,594	
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine					
• Symfi	600-mg/300-mg/150-mg tablet	30 tablets	$1,715	$2,057	N/A
• Symfi Lo	400-mg/300-mg/150-mg tablet	30 tablets	$1,715	$2,057	N/A
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Genvoya	150-mg/150-mg/10-mg/200-mg tablet	30 tablets	$3,584	$4,301	N/A
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Stribild	150-mg/150-mg/300-mg/ 200-mg tablet	30 tablets	$3,759	$4,511	N/A
Rilpivirine/Tenofovir Alafenamide/Emtricitabine					
• Odefsey	25-mg/25-mg/200-mg tablet	30 tablets	$3,262	$3,914	N/A
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Complera	25-mg/300-mg/200-mg tablet	30 tablets	$3,362	$3,914	N/A

Table 22b. Monthly Average Prices of Commonly Used Antiretroviral Drugs

Copackaged Combination Products as Injectable Regimens					
Cabotegravir + Rilpivirine					
• Cabenuva	600 mg (3 mL) 900 mg (3 mL)	2 vials	$6,088	$7,306	NA
• Cabenuva	400 mg (2 mL) 600 mg (2 mL)	2 vials	$4,059	$4,871	NA
PK Enhancers (Boosters)					
Cobicistat					
• Tybost	150-mg tablet	30 tablets	$268	$321	N/A
Ritonavir					
• Generic	100-mg tablet	30 tablets	$80 to $160	$278	$67
• Norvir	100-mg tablet	30 tablets	$257	$309	

[a] The following less commonly used ARV drugs are not included in this table: fosamprenavir and nelfinavir.

[b] Source: Micromedex Red Book [database]. IBM Watson Health. 2022. Available at: https://www.micromedexsolutions.com

[c] Source: Federal Upper Limits–March 2022 [database]. Medicare & Medicaid Services. 2022. Available at: https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html

Key: ADAP = AIDS Drug Assistance Program; ARV = antiretroviral; AWP = average wholesale price; CD4 = CD4 T lymphocyte; FUL = federal upper limit; HD = high dose; INSTI = integrase strand transfer inhibitor; N/A = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; SMAC = state maximum allowable cost; WAC = wholesale acquisition cost; XR = extended release

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Drug–Drug Interactions

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Overview

Pharmacokinetic (PK) drug–drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. In some instances, changes in drug exposure may increase the frequency and/or severity of toxicities or affect therapeutic responses. When prescribing or switching one or more drugs in an ARV regimen, clinicians must consider the potential for drug–drug interactions—both those affecting ARVs and those affecting concomitant drugs. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a specific drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways and drug transporter systems are prescribed concomitantly. When it is necessary to prescribe interacting drugs, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities. Tables 24a through 25b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modification of ARVs or concomitant medicines or for alternative therapy.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common drug interaction mechanisms are described and listed for individual ARV drugs in Table 23 below.

Pharmacokinetic Interactions Affecting Drug Absorption

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acid-reducing agents—such as proton pump inhibitors, H2 antagonists, or antacids—can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir and rilpivirine).
- Products that contain polyvalent cations—such as supplements, iron products, or antacids that contain aluminum, calcium, or magnesium—can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme cytochrome P450 (CYP) 3A4 or efflux transporter P-glycoprotein in the intestines may reduce or promote the absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are most frequently responsible for clinically significant drug interactions:

- The CYP450 enzyme system is responsible for the metabolism of many drugs, including non-nucleoside reverse transcriptase inhibitors, protease inhibitors, the CCR5 antagonist maraviroc, and the INSTI elvitegravir. CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARV drugs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
- The uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTIs cabotegravir and raltegravir. Drugs that induce or inhibit the UGT enzyme can affect the PKs of these INSTIs.
- The INSTIs bictegravir and dolutegravir (DTG) have mixed metabolic pathways, including both CYP3A4 and UGT1A1. Drugs that induce or inhibit these enzymes may have variable impact on the PKs of these INSTIs.

Pharmacokinetic Enhancers (Boosters)

PK enhancing is a strategy used to increase exposure of an ARV by concomitantly administering a drug that inhibits the enzymes that metabolize the ARV. Currently, two agents are used as PK enhancers: ritonavir (RTV) and cobicistat (COBI). Both drugs are potent inhibitors of the CYP3A4 enzyme and, thus, when coadministered with ARVs metabolized by the CYP3A4 pathway, the resultant systemic exposure of the ARVs is higher. Importantly, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. Complex or unknown mechanisms of PK-based interactions preclude extrapolation of RTV drug interactions to certain COBI interactions, such as interactions with warfarin, direct oral anticoagulants, phenytoin, voriconazole, oral contraceptives, and certain HMG-CoA reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

Drug transporters are expressed in various tissues, and they play an important role in drug disposition. Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic cation transporters in renal tubular cells. Similar transporters aid hepatic, renal, and biliary clearance of drugs and may be susceptible to drug interactions. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these drug transporters. The influence of drug transporters on drug–drug interactions is complex, and the clinical significance of these interactions is unclear but is under investigation. Further understanding of these pathways, and the clinical significance of this drug interaction mechanism is needed.

Role of Therapeutic Drug Monitoring in Managing Drug–Drug Interactions

Therapeutic drug monitoring (TDM) can guide the dosing of certain medications by using measured drug concentrations to improve the likelihood of desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

When concomitant use of an ARV drug and another medication is likely to result in a clinically important drug–drug interaction, the first step is to assess whether other, equally effective treatment options can be

used to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Drug concentration assays for some ARV drugs are commercially available; however, result reporting may take 1 week or longer. When interpreting assay results, clinicians should consider the patient's medication adherence, the timing of the patient's last ARV dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If needed, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take. If a dose adjustment is needed, TDM must be repeated after the dose-adjusted drug reaches steady state to assure appropriate dosing.

TDM information should not be used alone; it must be considered in conjunction with other clinical information—including virologic response, medication adherence, and signs and symptoms of drug toxicities—to assure safe and effective therapy.

Table 23. Mechanisms of Antiretroviral-Associated Drug Interactions

Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the antiretroviral (ARV) drug and/or the interacting drug. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and cytochrome P (CYP) 450– and uridine diphosphate glucuronosyltransferase (UGT) 1A1–mediated interactions.

Note: N/A indicates that there are no clinically relevant interactions by the mechanism. Identified mechanisms are specific to the ARV drugs described in the row and may not be reflective of complete ARV regimens. The older ARVs—fosamprenavir, nelfinavir, tipranavir, and zidovudine—are not commonly used in clinical practice and are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for these ARVs for information regarding 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
INSTIs							
BIC	N/A	Concentrations of PO agents are decreased by products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn).	Substrate	3A4	N/A	N/A	Substrate
CAB	N/A		Substrate	N/A	N/A	N/A	Substrate
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate
EVG/c	N/A		Inhibitor	3A4	3A4, 2D6	2C9	Substrate
RAL	N/A		N/A	N/A	N/A	N/A	Substrate
PIs							
ATV	Concentration decreased	N/A	Substrate, Inducer, Inhibitor	3A4	3A4, 2C8	N/A	Inhibitor
ATV/c	Concentration decreased	N/A	Substrate, Inhibitor	3A4	3A4, 2D6, 2C8	N/A	Inhibitor
ATV/r	Concentration decreased	N/A	Substrate, Inhibitor	3A4, 2D6	3A4, 2D6, 2C8	1A2, 2B6, 2C8, 2C9, 2C19	ATV: Inhibitor RTV: Inducer

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
PIs (continued)							
DRV/c	N/A	N/A	Substrate, effect on P-gp unknown	3A4	3A4, 2D6	N/A	No data
DRV/r	N/A	N/A	Substrate, effect on P-gp unknown	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
NVP	N/A	N/A	N/A	3A4, 2B6	N/A	3A4, 2B6	N/A
RPV	Only RPV PO: Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A
NRTIs							
ABC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
CCR5 Antagonist							
MVC	N/A	N/A	Substrate	3A4	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
gp120–Directed Attachment Inhibitor							
FTR	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
Fusion Inhibitor							
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; Ca = calcium; CAB = cabotegravir; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; FTR = fostemsavir; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; P-gp = P-glycoprotein; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase; Zn = zinc

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Updated: September 01, 2022
Reviewed: September 01, 2022

This table provides information on the known or predicted interactions between protease inhibitors (PIs) and non-antiretroviral (ARV) drugs. When information is available, interactions for boosted atazanavir (ATV) (with either ritonavir [RTV] or cobicistat [COBI]) and unboosted ATV are listed separately. The term "all PIs" refers to both unboosted ATV and ATV, darunavir (DRV), and lopinavir (LPV) boosted with either RTV or COBI. This table does not include interactions for fosamprenavir (FPV), nelfinavir (NFV), or tipranavir (TPV). For information regarding interactions between PIs and other ARV drugs, including dosing recommendations, refer to Tables 24c, 25a, and 25b.

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Note: FPV, NFV, and TPV are no longer commonly used in clinical practice and are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions between these PIs and concomitant medications.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV (unboosted), ATV/c, ATV/r	When Given Simultaneously • ↓ ATV expected	Administer ATV at least 2 hours before or 2 hours after antacids or buffered medications.
H2 Receptor Antagonists	ATV (unboosted)	When Given Simultaneously With Famotidine • ATV AUC ↓ 41% When Given 2 Hours Before and **≥10** Hours After H2RA • ↔ ATV	A single dose of H2RA should not exceed a dose equivalent to famotidine 20 mg, and the total daily dose should not exceed a dose equivalent to famotidine 20 mg twice daily in PI-naive patients. Give ATV with food at least 2 hours before and at least 10 hours after the H2RA. Do not coadminister unboosted ATV plus H2RA in PI-experienced patients.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ATV/c, ATV/r	↓ ATV expected	H2RA dose should not exceed a dose equivalent to famotidine 40 mg twice daily in ART-naive patients or famotidine 20 mg twice daily in ART-experienced patients. Give ATV 300 mg (plus COBI 150 mg or RTV 100 mg) with food simultaneously with and/or ≥10 hours after the dose of H2RA. If using TDF and H2RA in ART-experienced patients, administer ATV 400 mg plus RTV 100 mg with food simultaneously with and/or ≥10 hours after the dose of H2RA. Do not coadminister ATV/c with TDF and H2RA in ART-experienced patients.
	DRV/c, DRV/r, LPV/r	With Ranitidine • ↔ DRV/r ↔ PI expected	No dose adjustment needed.
Proton Pump Inhibitors	ATV (unboosted)	**With Omeprazole 40 mg** • ATV AUC ↓ 94%	Do not coadminister.
	ATV/c, ATV/r	**With Omeprazole 40 mg** • ATV AUC ↓ 76% **When Omeprazole 20 mg** Is Given **12** Hours Before ATV/c or ATV/r • ATV AUC ↓ 42%	PPI dose should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r. Do not coadminister in PI-experienced patients.
	DRV/c, LPV/r	↔ PI expected	No dose adjustment needed.
	DRV/r	↔ DRV/r Omeprazole AUC ↓ 42%	Consider alternative ARV or acid reducer. If coadministered, monitor for omeprazole efficacy. If the patient does not experience symptomatic relief, increase the dose to no more than omeprazole 40 mg daily.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	All PIs	↑ alfuzosin expected	Contraindicated.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Doxazosin	All PIs	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/adverse events. Dose reduction may be necessary.
Tamsulosin	All PIs	↑ tamsulosin expected	Do not coadminister unless benefits outweigh risks. If coadministered, monitor for tamsulosin-related adverse events.
Terazosin	All PIs	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/adverse events. Dose reduction may be necessary.
Silodosin	All PIs	↑ silodosin expected	Contraindicated.
Antibacterials—Antimycobacterials			
Bedaquiline	All PIs	With LPV/r • Bedaquiline AUC ↑ 1.9-fold With Other PI/r, ATV/c, or DRV/c • ↑ bedaquiline possible	Do not coadminister unless benefits outweigh risks. Monitor liver function and ECG for QTc prolongation.
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Recommended dose is rifabutin 150 mg once daily. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. Monitor for rifabutin-related adverse events, including neutropenia and uveitis. PK data in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants.
	ATV/r	Compared With **Rifabutin (300 mg Once Daily) Alone, Rifabutin (150** mg Once Daily) Plus ATV/r • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	
	DRV/r	Compared With **Rifabutin (300 mg Once Daily) Alone, Rifabutin (150** mg Every Other Day) Plus DRV/r • ↔ rifabutin AUC and metabolite AUC ↑ 881%	

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	LPV/r	Compared W**ith Rifabutin (300 mg Daily) Alone, Rifabutin (150 mg Once** Daily) Plus LPV/r • Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%	
	PI/c	↑ rifabutin expected ↓ COBI expected	Do not coadminister.
Rifampin	All PIs	↓ PI concentration by >75%	Contraindicated. Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. Increasing the COBI dose is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	Do not coadminister.
Antibacterials—Macrolides			
Azithromycin	ATV (unboosted), ATV/c, ATV/r	↑ azithromycin possible	No dose adjustment needed.
	DRV/c, DRV/r	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	ATV (unboosted)	Clarithromycin AUC ↑ 94% ATV ↑ 28%	Reduce clarithromycin dose by 50% or consider alternative ARV or azithromycin. Monitor for clarithromycin-related adverse events, including QTc prolongation.
	ATV/r, PI/c	↑ clarithromycin expected ↑ ATV/r and PI/c expected	Consider alternative ARV or azithromycin.
	DRV/r, LPV/r	DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg twice daily ↑ clarithromycin 77%	Consider alternative ARV or azithromycin. If use of clarithromycin is necessary in a patient with impaired renal function, reduce clarithromycin dose by 50% in patients with CrCl 30 to 60 mL/min. In patients with CrCl <30 mL/min, reduce clarithromycin dose by 75%. Monitor for clarithromycin-related adverse events, including QTc prolongation.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Erythromycin	All PIs	↑ erythromycin expected ↑ PIs expected	Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	ATV (unboosted)	↑ apixaban possible	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	PI/c, PI/r	↑ apixaban expected	Do not coadminister in patients who require apixaban 2.5 mg twice daily. **In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily** • Reduce apixaban dose by 50%.
Dabigatran	ATV (unboosted), DRV/c, DRV/r, LPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r	**With COBI 150 mg Alone** • Dabigatran AUC ↑ 110% to 127% With ATV/r • ↑ dabigatran expected	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instructions when using dabigatran concomitantly with P-glycoprotein inhibitors.
Edoxaban	ATV (unboosted), DRV/c, DRV/r, LPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/r, ATV/c	↑ edoxaban expected	Stroke Prevention in Nonvalvular Atrial Fibrillation Indication • No dose adjustment needed. Deep Venous Thrombosis and Pulmonary Embolism Indication • Administer edoxaban 30 mg once daily.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rivaroxaban	ATV (unboosted)	↑ rivaroxaban possible	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	PI/c, PI/r	↑ rivaroxaban expected	Do not coadminister.
Warfarin	PI/c	No data	Monitor INR closely when stopping or starting PI/c or PI/r and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.
	PI/r	↓ warfarin possible	
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI concentrations substantially	Do not coadminister.
	ATV/r, LPV/r	↑ carbamazepine possible May ↓ PI concentrations substantially	Consider alternative ARV or anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assess virologic response. Carbamazepine dose reduction may be necessary. Do not coadminister with LPV/r once daily.
	DRV/r	Carbamazepine AUC ↑ 45% ↔ DRV	Monitor anticonvulsant concentration and adjust dose accordingly.
	PI/c	↑ carbamazepine possible ↓ COBI expected ↓ PI expected	Contraindicated.
Eslicarbazepine	All PIs	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Ethosuximide	All PIs	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	ATV (unboosted)	↔ lamotrigine	No dose adjustment needed.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; monitor lamotrigine concentration or consider alternative ARV or anticonvulsant.
	LPV/r	Lamotrigine AUC ↓ 50% ↔ LPV	
	DRV/r	↓ lamotrigine possible	
	PI/c	No data	Monitor anticonvulsant concentration and adjust dose accordingly.
Oxcarbazepine	All PIs	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Phenobarbital	ATV (unboosted)	↓ ATV expected	Do not coadminister.
	ATV/r, DRV/r	↓ phenobarbital possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	LPV/r	↓ phenobarbital possible ↓ LPV/r possible	Do not coadminister with LPV/r once daily. Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	PI/c	↓ COBI expected ↓ PI expected	Contraindicated.
Phenytoin	ATV (unboosted)	↓ ATV expected	Do not coadminister.
	ATV/r, DRV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	LPV/r	Phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Do not coadminister with LPV/r once daily. Consider alternative anticonvulsant or monitor concentrations of both drugs and assess virologic response.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	PI/c	↓ COBI expected ↓ PI expected	Contraindicated.
Valproic Acid	All PIs	↓ or ↔ VPA possible LPV AUC ↑ 38% No data for other PIs	Monitor VPA concentrations and monitor for PI tolerability.
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below			
Bupropion	ATV (unboosted)	↔ bupropion expected	No dose adjustment needed.
	ATV/r, DRV/r	↓ bupropion possible	Titrate bupropion dose based on clinical response.
	LPV/r	Bupropion AUC ↓ 57%	
	PI/c	↔ bupropion expected	No dose adjustment needed.
Buspirone	All PIs	↑ buspirone expected	Administer lowest dose of buspirone with caution and titrate buspirone dose based on clinical response. Dose reduction may be necessary. Monitor for buspirone-related adverse events.
Nefazodone	All PIs	↑ nefazodone expected ↑ PI possible	Monitor for nefazodone-related adverse events and PI tolerability.
Trazodone	All PIs	**RTV 200 mg twice daily (for 2 days)** • Trazodone ↑ AUC 240%	Administer lowest dose of trazodone and monitor for CNS and CV adverse events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Tricyclic Antidepressants Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine	All PIs	↑ TCA expected	Administer lowest possible TCA dose and titrate based on clinical assessment and/or drug concentrations. Monitor for TCA-related adverse events.
Selective Serotonin Reuptake Inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response.
	All PIs except DRV/r	No data	Titrate SSRI dose using the lowest available initial or maintenance dose.
Antipsychotics			
Aripiprazole	ATV (unboosted)	↑ aripiprazole expected	Administer 50% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	PI/c, PI/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Brexpiprazole	ATV (unboosted)	↑ brexpiprazole expected	Administer 50% of the usual brexpiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	PI/c, PI/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate the dose based on clinical monitoring for efficacy/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cariprazine	All PIs	↑ cariprazine expected	Starting Cariprazine in a Patient Who Is Already Receiving a PI • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased. Starting a PI in a Patient Who Is Already Receiving Cariprazine • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce the dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, the cariprazine dose may need to be increased.
Iloperidone	All PIs	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lumateperone	All PIs	↑ lumateperone expected	Do not coadminister.
Lurasidone	ATV (unboosted)	↑ lurasidone expected	Consider alternative ARV or antipsychotic. If coadministration is necessary and atazanavir is added to lurasidone therapy, reduce lurasidone dose by 50%. If coadministration is necessary and lurasidone is added to ATV therapy, the recommended starting dose of lurasidone is 20 mg daily and the maximum recommended dose is 80 mg daily.
	PI/c, PI/r	↑ lurasidone expected	Contraindicated.
Olanzapine	ATV (unboosted), PI/c	↔ olanzapine expected	No dose adjustment needed.
	PI/r	↓ olanzapine possible	Monitor for therapeutic effectiveness of olanzapine.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., clozapine, perphenazine, risperidone, thioridazine)	PI/c, PI/r	↑ antipsychotic possible	Titrate the antipsychotic dose using the lowest initial dose or adjust the maintenance dose accordingly. Monitor for adverse events, including QTc prolongation.
Pimavanserin	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or antipsychotic.
	LPV/r	↑ pimavanserin expected	Do not coadminister, due to risk for QTc prolongation.
	All other PIs	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg once daily.
Pimozide	All PIs	↑ pimozide expected	Contraindicated.
Quetiapine	All PIs	↑ quetiapine expected	Starting Quetiapine in a Patient Receiving a PI • Initiate quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse events, including QTc prolongation. Starting a PI in a Patient Receiving a Stable Dose of Quetiapine • Consider alternative ARV. If coadministered, reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine effectiveness and adverse events, including QTc prolongation.
Ziprasidone	LPV/r	↑ ziprasidone expected	Do not coadminister, due to risk for QTc prolongation.
	All other PIs	↑ ziprasidone expected	Monitor for ziprasidone-related adverse events, including QTc prolongation.
Antifungals			
Fluconazole	All PIs	↔ PI expected ↔ fluconazole expected	No dose adjustment needed.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%	If coadministered, monitor isavuconazole concentrations and adverse events. Monitor for virologic response.
	All PIs except LPV/r	↑ isavuconazole expected ↑ PI possible	If coadministered, monitor isavuconazole concentrations and monitor for isavuconazole-related adverse events. Monitor for PI tolerability.
Itraconazole	ATV (unboosted)	↑ itraconazole expected	Dose based on itraconazole concentrations and monitor for itraconazole-related adverse events.
	PI/r, PI/c	↑ itraconazole expected ↑ PI expected	Itraconazole doses >200 mg/day are not recommended unless dosing is guided by itraconazole concentrations.
Posaconazole	ATV (unboosted)	ATV AUC ↑ 268% ↑ or ↓ posaconazole possible	If coadministered, monitor posaconazole concentrations and monitor for posaconazole-related or PI-related adverse events.
	ATV/r	ATV AUC ↑ 146% ↑ posaconazole possible	
	All other PIs	↑ PI expected ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ or ↓ PI possible ↑ or ↓ voriconazole possible	If coadministered, monitor voriconazole concentrations and monitor for voriconazole-related or PI-related adverse events.
	PI/c	No data	Do not coadminister voriconazole and RTV or COBI unless benefits outweigh risks. If coadministered, monitor voriconazole concentration and adjust dose accordingly.
	PI/r	RTV 100 mg twice daily ↓ voriconazole AUC 39%	

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials			
Artemether/Lumefantrine	ATV (unboosted), PI/c	↑ lumefantrine expected No data for artemether	Clinical significance is unknown. If coadministered, monitor closely for antimalarial efficacy and lumefantrine-related adverse events, including QTc prolongation.
	DRV/r	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 175% ↔ DRV	
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 45% Lumefantrine AUC ↑ 4.8-fold ↔ LPV	
Atovaquone/Proguanil	ATV/r, LPV/r	With ATV/r • Atovaquone AUC ↓ 46% • Proguanil AUC ↓ 41% With LPV/r • Atovaquone AUC ↓ 74% • Proguanil AUC ↓ 38%	Clinical significance is unknown. Consider alternative ARV or malaria prophylaxis.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Mefloquine	All PIs	**With RTV 200 mg Twice Daily** • RTV AUC ↓ 31% and C_{min} ↓ 43% • ↔ mefloquine With ATV (Unboosted), PI/c, or PI/r • No data • ↑ mefloquine possible	Clinical significance is unknown. Consider alternative ARV or antimalarial drug. If coadministered, monitor for mefloquine-related adverse events, including psychiatric symptoms and QTc prolongation. Monitor virologic response.
Antiplatelets			
Clopidogrel	All boosted PIs	Clopidogrel active metabolite AUC ↓ 69% in people with HIV compared to healthy volunteers without HIV. Impaired platelet inhibition observed in people with HIV.	Do not coadminister.
Prasugrel	All boosted PIs	Prasugrel active metabolite AUC ↓ 52% in people with HIV compared to healthy volunteers without HIV. Adequate platelet inhibition observed in people with HIV.	No dose adjustment needed.
Ticagrelor	All PIs	↑ ticagrelor expected	Do not coadminister.
Vorapaxar	All PIs	↑ vorapaxar expected	Do not coadminister.
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone Oral suspension	ATV/r	↔ atovaquone	No dose adjustment needed.
	All other PIs	↔ atovaquone expected	No dose adjustment needed.
Antivirals—Orthopoxviruses (Mpox, Smallpox)			
Brincidofovir	All PIs	↑ brincidofovir possible	Give PI dose at least 3 hours after administering brincidofovir and monitor for brincidofovir-related adverse events (i.e., elevations in ALT/AST and bilirubin and GI adverse events).

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cidofovir	All PIs	↔ cidofovir	No dose adjustment needed.
Tecovirimat	All PIs	↔ tecovirimat	No dose adjustment needed.
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	ATV (unboosted), ATV/c, ATV/r	↑ arformoterol possible	No dose adjustment needed.
	DRV/c, DRV/r, LPV/r	↔ arformoterol expected	No dose adjustment needed.
Indacaterol	All PIs	With RTV **300 mg Twice Daily** • Indacaterol AUC ↑ 1.7-fold	No dose adjustment needed in patients receiving indacaterol 75 mcg daily.
Olodaterol	All PIs	↑ olodaterol expected	No dose adjustment needed.
Salmeterol	All PIs	↑ salmeterol possible	Do not coadminister, due to potential increased risk of salmeterol-related CV events.
Cardiac Medications			
Amiodarone	ATV/r	↑ amiodarone possible ↑ PI possible	Contraindicated.
	All other PIs	↑ amiodarone possible ↑ PI possible	Do not coadminister unless the benefits outweigh the risks. If coadministered, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone drug concentration.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor for antiarrhythmic-related adverse events.
	PI/c, PI/r	↑ antiarrhythmic possible	Do not coadminister.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Dronedarone	ATV (unboosted)	↑ dronedarone possible	Do not coadminister.
	PI/c, PI/r	↑ dronedarone expected	Contraindicated.
Flecainide	All PIs	↑ flecainide possible	Do not coadminister.
Propafenone	All PIs	↑ propafenone possible	Do not coadminister.
Quinidine	ATV/r	↑ quinidine expected	Contraindicated.
	All other PIs	↑ quinidine possible	Do not coadminister.
Beta-Blockers (e.g., carvedilol, metoprolol, timolol)	All PIs	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP2D6 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
Bosentan	All PIs	With LPV/r • ↑ bosentan 48-fold (Day 4) and ↑ 5-fold (Day 10) With other PI ↑ bosentan expected With ATV (unboosted) ↓ ATV expected	Do not coadminister bosentan and unboosted ATV. **In Patients on a PI (Other Than Unboosted ATV) >10** Days • Start bosentan at 62.5 mg once daily or every other day. In Patients on Bosentan Who Require a PI (Other Than Unboosted ATV) • Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day. When Switching Between COBI and RTV • Maintain same bosentan dose.
Calcium Channel Blockers, Except Diltiazem	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Digoxin	PI/c, PI/r	RTV 200 mg twice daily ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41% and ↔ AUC	Monitor digoxin concentrations. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV (unboosted), ATV/c, ATV/r	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ of diltiazem AUC is likely with ATV/c or ATV/r	Decrease diltiazem dose by at least 50%. If starting diltiazem, start with the lowest dose and titrate according to clinical response and adverse events. ECG monitoring is recommended.
	DRV/c, DRV/r, LPV/r	↑ diltiazem possible	Titrate diltiazem dose according to clinical response and adverse events.
Eplerenone	PI/c, PI/r	↑ eplerenone expected	Contraindicated.
Ranolazine	ATV (unboosted)	↑ ranolazine possible	Do not coadminister.
	PI/c, PI/r	↑ ranolazine expected	Contraindicated.
Ivabradine	All PIs	↑ ivabradine expected	Contraindicated.
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg twice daily ↑ 17-BMP AUC 2-fold	No dose adjustment needed.
	All PIs except DRV/r	↔ 17-BMP expected	No dose adjustment needed.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg twice daily ↑ fluticasone AUC 350-fold	Do not coadminister unless the potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse events associated with corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider alternative inhaled/intranasal corticosteroid (e.g., beclomethasone).

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Do not coadminister unless the potential benefits of systemic corticosteroid outweigh the risks of adverse events associated with systemic corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	LPV/r	↑ prednisolone AUC 31%	Coadministration may be considered if the potential benefits outweigh the risks of adverse events associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-related adverse events.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	All PIs	↑ glucocorticoids expected	Do not coadminister. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Glucose-Lowering Medications			
Canagliflozin	ATV (unboosted), PI/c	↔ canagliflozin	No dose adjustment needed.
	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, increase canagliflozin dose to 200 mg daily. If a patient is already tolerating canagliflozin 200 mg daily and requires additional glycemic control, management strategy is based on renal function. **In Patients with eGFR ≥60 mL/min/1.73 m^2** • Canagliflozin dose may be increased to 300 mg daily. **In Patients with eGFR <60 mL/min/1.73 m^2** • Consider adding another antihyperglycemic agent.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/Saxagliptin	All PIs	↑ saxagliptin expected	Do not coadminister. Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination is not recommended.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c, ATV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	ATV (unboosted), DRV/c, DRV/r, LPV/r	↔ daclatasvir	No dose adjustment needed.
Dasabuvir plus Paritaprevir/Ombitasvir/ RTV	ATV (unboosted)	↔ ATV	ATV 300 mg alone, without COBI or additional RTV, should be given in the morning with dasabuvir plus paritaprevir/ombitasvir/RTV.
	ATV/c, ATV/r	No data	This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg daily without COBI or RTV. ATV should be administered in the morning, at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.
	DRV	DRV C_{min} ↓ 43% to 48%	Do not coadminister.
	LPV/r	Paritaprevir AUC ↑ 117%	Do not coadminister.
	DRV/c	No data	Do not coadminister.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Elbasvir/Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold Elbasvir ↔ ATV Grazoprevir ↑ ATV AUC 43%	Contraindicated. May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
	DRV/r	Elbasvir AUC ↑ 66% Grazoprevir AUC ↑ 7.5-fold ↔ DRV	
	LPV/r	Elbasvir AUC ↑ 3.7-fold Grazoprevir AUC ↑ 12.9-fold ↔ LPV	
	ATV (unboosted), ATV/c, DRV/c	↑ grazoprevir expected	
Glecaprevir/Pibrentasvir	ATV (unboosted), ATV/c, ATV/r	**With (ATV 300 mg plus RTV 100 mg)** Once Daily • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	Contraindicated.
	DRV/c, DRV/r	**With (DRV 800 mg plus RTV 100 mg)** Once Daily • Glecaprevir AUC ↑ 5-fold • ↔ pibrentasvir	Do not coadminister.
	LPV/r	Glecaprevir AUC ↑ 4-fold Pibrentasvir ↑ 2.5-fold	Do not coadminister.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Ledipasvir/Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose adjustment needed. Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased risk of TDF toxicities. If coadministration is necessary, monitor for TDF-related adverse events.
	ATV (unboosted), ATV/c, DRV/c, DRV/r, LPV/r	↔ PI expected ↔ ledipasvir and sofosbuvir	
Sofosbuvir/Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment needed.
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓ 28% ↔ velpatasvir	No dose adjustment needed.
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ sofosbuvir and velpatasvir expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir/ Voxilaprevir	ATV (unboosted), ATV/c, ATV/r	With ATV/r • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	Do not coadminister.
	LPV/r	↑ voxilaprevir expected	Do not coadminister.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	DRV/c, DRV/r	With DRV/r • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed.
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	Contraindicated.
Hormonal Therapies			
Contraceptives—Injectable Depot MPA	LPV/r	MPA AUC ↑ 46%	No dose adjustment needed.
	All other PIs	No data	No dose adjustment needed.
Contraceptives—Oral	ATV (unboosted)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Prescribe an oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[b] or use alternative ARV or contraceptive methods. Oral contraceptives that contain less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	ATV/c	Drosperinone AUC ↑ 130% Ethinyl estradiol AUC ↓ 22%	Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia. Use alternative ARV or contraceptive methods.
		↔ ethinyl estradiol AUC and C_{min} ↓ 25% ↔ levonorgestrel	No dose adjustment needed.
	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate AUC ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[c]

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	DRV/c	Drospirenone AUC ↑ 58% Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods.
	DRV/r	Ethinyl estradiol AUC ↓ 44% and C_{min} ↓ 62% Norethindrone AUC ↓ 14% and C_{min} ↓ 30%	When Used for Contraception • Consider alternative ARV or contraceptive methods. If combined, consider using an oral contraceptive with at least 35 mcg of ethinyl estradiol. When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation) • Monitor for clinical effectiveness of hormonal therapy.
	LPV/r	Ethinyl estradiol AUC ↓ 42% and C_{min} ↓ 32% to 58% Norethindrone AUC ↓ 17% and C_{min} ↓ 32% ↔ C_{min} etonogestrel (metabolite of oral desogestrel)	Consider using an oral contraceptive with at least 35 mcg of ethinyl estradiol.
Contraceptives—Subdermal Implant Etonogestrel	LPV/r	Etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	No dose adjustment needed.
	All other PIs	↑ etonogestrel expected	
Contraceptives—Subdermal Implant Levonorgestrel	All PIs	↑ levonorgestrel expected	No dose adjustment needed.
Contraceptives—Transdermal Ethinyl Estradiol/Norelgestromin	LPV/r	↔ LPV Ethinyl estradiol AUC ↓ 45% Norelgestromin AUC ↑ 83%	No dose adjustment needed.
	All other PIs	No data	

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Contraceptives—Vaginal Ring Etonogestrel/Ethinyl Estradiol	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	No dose adjustment needed.
	All other PIs	No data	
Contraceptives—Vaginal Ring Segesterone/Ethinyl Estradiol	All PIs	No data	Use alternative ARV or contraceptive methods.
Emergency Contraceptives Levonorgestrel (oral)	All PIs	↑ levonorgestrel expected	No dose adjustment needed.
Gender-Affirming Therapy	PI/c	↑ estradiol possible	Adjust estradiol dose as needed based on clinical effects and endogenous hormone concentrations.
	PI/r	↓ or ↑ estradiol possible	
	All PIs	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed.
	All PIs	↑ dutasteride possible ↑ finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations. No dose adjustment needed for finasteride.
	All PIs	↑ testosterone possible	Adjust testosterone dose as needed based on clinical effects and endogenous hormone concentrations.
Menopausal Hormone Replacement Therapy	All PIs	↓ or ↑ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)	Adjust estrogen dose as needed based on clinical effects.
	All PIs	↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See the different Contraceptives entries for other progestin-PI interactions	Adjust progestin/progesterone dose as needed based on clinical effects. Drospirenone is not contraindicated with ATV/c products, because it is prescribed at a lower dose for menopausal HRT than products used for hormonal contraceptives.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Immunosuppressants			
Cyclosporine, Sirolimus, Tacrolimus	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Everolimus	DRV/c, DRV/r	↑ immunosuppressant expected	Do not coadminister.
	All other PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	ATV (unboosted), ATV/r	↑ atorvastatin possible	Administer the lowest effective atorvastatin dose while monitoring for adverse events.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold and C_{max} ↑ 18.9-fold	Do not coadminister.
	DRV/c	Atorvastatin AUC ↑ 3.9-fold and C_{max} ↑ 4.2-fold	Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
	LPV/r	Atorvastatin AUC ↑ 5.9-fold and C_{max} ↑ 4.7-fold	Administer the lowest effective atorvastatin dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
Lomitapide	All PIs	↑ lomitapide expected	Contraindicated.
Lovastatin	All PIs	Significant ↑ lovastatin expected	Contraindicated.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Pitavastatin	All PIs	With Unboosted ATV • ↑ pitavastatin AUC 31% and C_{max} ↑ 60% • ↔ ATV With DRV/r • ↓ pitavastatin AUC 26% • ↔ DRV/r With LPV/r • ↓ pitavastatin AUC 20% • ↔ LPV	No dose adjustment needed.
Pravastatin	ATV (unboosted), ATV/c, ATV/r	No data	Administer the lowest effective pravastatin dose while monitoring for adverse events.
	DRV/c, DRV/r	With DRV/r • Pravastatin AUC ↑ 81% following single dose of pravastatin • Pravastatin AUC ↑ 23% at steady state	Administer the lowest effective pravastatin dose while monitoring for adverse events.
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment needed.
Rosuvastatin	ATV (unboosted)	↑ rosuvastatin expected	Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 10 mg daily.
	ATV/r	Rosuvastatin AUC ↑ 3-fold and C_{max} ↑ 7-fold	
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold and C_{max} ↑ 10.6-fold	

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold and C_{max} ↑ 3.8-fold	Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 20 mg daily.
	DRV/r	Rosuvastatin AUC ↑ 48% and C_{max} ↑ 2.4-fold	Administer the lowest effective rosuvastatin dose while monitoring for adverse events.
	LPV/r	Rosuvastatin AUC ↑ 2.1-fold and C_{max} ↑ 4.7-fold	Administer the lowest effective rosuvastatin dose while monitoring for adverse events. Do not exceed rosuvastatin 10 mg daily.
Simvastatin	All PIs	Significant ↑ simvastatin expected	Contraindicated.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV (unboosted)	Buprenorphine AUC ↑ 93% Norbuprenorphine (active metabolite) AUC ↑ 76% ↓ ATV possible	Do not coadminister.
	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 105%	Monitor for sedation and other signs or symptoms of overmedication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	DRV/r	↔ buprenorphine Norbuprenorphine (active metabolite) AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment needed. Monitor for buprenorphine-related adverse events. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	LPV/r	↔ LPV/r	
	PI/c	No data	Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Monitor for buprenorphine-related adverse events.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Fentanyl	All PIs	↑ fentanyl possible	Monitor for fentanyl-related adverse events, including potentially fatal respiratory depression.
Lofexidine	ATV (unboosted)	↔ lofexidine expected	No dose adjustment needed.
	PI/c, PI/r	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	ATV (unboosted)	↔ ATV	No dose adjustment needed.
	PI/c	No data	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Monitor for methadone-related adverse events.
	All PI/r	ATV/r and DRV/r ↓ R-methadone[d] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53%	Opioid withdrawal is unlikely but may occur. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Oxycodone	All PIs	LPV/r ↑ oxycodone AUC 2.6-fold Other PIs: ↑ oxycodone expected	Monitor for opioid-related adverse events, including potentially fatal respiratory depression. Oxycodone dose reduction may be necessary.
Tramadol	All PIs	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.
PDE5 Inhibitors			
Avanafil	ATV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
	PI/c, PI/r	RTV 600 mg twice daily (for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	Do not coadminister.
Sildenafil	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone	For Treatment of Erectile Dysfunction • Start with sildenafil 25 mg every 48 hours and monitor for adverse events of sildenafil.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		RTV 500 mg twice daily ↑ sildenafil AUC 1,000%	Contraindicated for treatment of PAH.
Tadalafil	All PIs	RTV 200 mg twice daily ↑ tadalafil AUC 124%	For Treatment of Erectile Dysfunction • Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse events of tadalafil. For Treatment of PAH *In Patients on a PI >7 Days* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil Who Require a PI* • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients Switching Between COBI and RTV* • Maintain tadalafil dose. For Treatment of Benign Prostatic Hyperplasia • Maximum recommended daily dose is tadalafil 2.5 mg per day.
Vardenafil	All PIs	RTV 600 mg twice daily ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse events of vardenafil.

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sedative/Hypnotics			
Alprazolam, Clonazepam, Diazepam	All PIs	↑ benzodiazepine possible RTV 200 mg twice daily (for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248%	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
Lorazepam, Oxazepam, Temazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways and, therefore, have less interaction potential than other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected	Oral midazolam is contraindicated with PIs. Parenteral midazolam can be used with caution when given in a monitored situation with appropriate medical management available in case of respiratory sedation and/or prolonged sedation. Consider dose reduction, especially if more than a single dose of midazolam is administered.
Suvorexant	All PIs	↑ suvorexant expected	Do not coadminister.
Triazolam	All PIs	↑ triazolam expected RTV 200 mg twice daily ↑ triazolam half-life 1,200% and ↑ AUC 2,000%	Contraindicated.
Zolpidem	PI/c, PI/r	↑ zolpidem possible	Initiate zolpidem at a low dose and monitor for zolpidem-related adverse events. Dose reduction may be necessary.
Miscellaneous Drugs			
Calcifediol	All PIs	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored.
Cisapride	All PIs	↑ cisapride expected	Contraindicated.
Colchicine	All PIs	RTV 100 mg twice daily ↑ colchicine AUC 296% and C_{max} ↑ 184%	For Treatment of Gout Flares

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		Significant ↑ colchicine expected with all PIs, with or without COBI or RTV	• Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. For Treatment of Familial Mediterranean Fever • Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg twice daily. Contraindicated in patients with hepatic (Child-Pugh Score A, B, or C) or renal impairment (CrCl <60 mL/min).
Dronabinol	All PIs	↑ dronabinol possible	Monitor for dronabinol-related adverse events.
Eluxadoline	All PIs	↑ eluxadoline expected	Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse events.
Ergot Derivatives	All PIs	↑ dihydroergotamine, ergotamine, and methylergonovine expected	Contraindicated.
Flibanserin	All PIs	↑ flibanserin expected	Contraindicated.

[a] DHA is an active metabolite of artemether.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations also may be available.

[c] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl. Generic formulations also may be available.

[d] R-methadone is the active form of methadone.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma

Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs

concentration; CCB = calcium channel blocker; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EVG/c = elvitegravir/cobicistat; GI = gastrointestinal; H2RA = H2 receptor antagonist; HCV = hepatitis C virus; HRT = hormone replacement therapy; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; VPA = valproic acid

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Updated: September 01, 2022
Reviewed: September 01, 2022

This table provides information on the known or predicted interactions between non-nucleoside reverse transcriptase inhibitors (NNRTIs) and non-antiretroviral (ARV) drugs. Cabotegravir (CAB) intramuscular (IM) plus rilpivirine (RPV) IM are co-packaged into a single product and are coadministered as a complete regimen; therefore, the dosing recommendations and clinical comments reflect the combination of CAB IM and RPV IM treatments. Drug interaction studies were not conducted with either CAB IM or RPV IM. Drug interaction studies with oral CAB and RPV were leveraged to make the dosing recommendations for CAB IM and RPV IM. For information regarding interactions between NNRTIs and other ARV drugs, including dosing recommendations, refer to Tables 24c, 24e, 24f, 25a, and 25b.

Recommendations for managing a particular drug interaction may differ, depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. When an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgment to select the most appropriate alternative medication to use.

RPV 75 mg and 300 mg oral once daily (3 and 12 times the recommended dose, respectively) were shown to prolong the QTc interval. Known and expected/theoretical pharmacokinetic interactions, resulting in increased RPV exposures, are included in this table due to the safety concern of QTc prolongation. There is limited information about the potential for pharmacodynamic interactions between RPV (in the absence of increased RPV exposures) and drugs that prolong the QTc interval; therefore, these are not included in this table.

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	DOR, EFV, NVP	↔ NNRTI AUC	No dose adjustment needed.
	ETR	↔ ETR expected	No dose adjustment needed.
	RPV IM	↔ RPV expected	No dose adjustment needed.
	RPV PO	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	DOR, NVP	↔ NNRTI expected	No dose adjustment needed.
	EFV	↔ EFV AUC	No dose adjustment needed.
	ETR	↔ ETR AUC	No dose adjustment needed.
	RPV IM	↔ RPV expected	No dose adjustment needed.
	RPV PO	RPV AUC ↓ 76% when famotidine 40 mg is taken 2 hours prior	Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Proton Pump Inhibitors	DOR	DOR AUC ↓ 17% and C_{min} ↓ 16%	No dose adjustment needed.
	EFV, NVP	↔ EFV and NVP expected	
	ETR	With Omeprazole 40 mg Daily ETR AUC ↑ 41%	
	RPV IM	↔ RPV expected	No dose adjustment needed.
	RPV PO	With Omeprazole 20 mg Daily RPV AUC ↓ 40% and C_{min} ↓ 33%	Contraindicated.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin,Doxazosin, Silodosin, Terazosin	DOR, RPV IM, RPV PO	↔ alpha-adrenergic antagonists expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ alpha-adrenergic antagonists expected	Consider alternative ARV or alpha-antagonist therapy. If coadministration is necessary, monitor for therapeutic effectiveness of alpha antagonist.
Tamsulosin	DOR, RPV IM, RPV PO	↔ tamsulosin expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ tamsulosin expected	Monitor for therapeutic effectiveness of tamsulosin after 2–4 weeks. May need to increase dose to tamsulosin 0.8 mg once daily for patients who fail to respond to the 0.4-mg dose.
Antimycobacterials			
Bedaquiline	DOR, RPV IM, RPV PO	↔ bedaquiline expected	No dose adjustment needed.
	EFV, ETR	↓ bedaquiline possible	Do not coadminister.
	NVP	↔ bedaquiline AUC	No dose adjustment needed.
Rifabutin	DOR	DOR AUC ↓ 50%	Increase DOR dose to 100 mg twice daily. No dose adjustment is needed for rifabutin.
	EFV	Rifabutin ↓ 38%	The recommended dosing range is rifabutin 450–600 mg per day.
	ETR	↔ rifabutin and metabolite AUC ETR AUC ↓ 37%	Do not coadminister ETR plus PI/r with rifabutin. Use rifabutin 300 mg once daily if ETR is administered without PI/r.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dose adjustment needed.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RPV IM	↓ RPV expected	Contraindicated.
	RPV PO	Rifabutin plus RPV 50 mg PO Once Daily Compared to RPV 25 mg Once Daily Alone ↔ RPV AUC and C_{min}	Increase RPV dose to 50 mg PO once daily. No dose adjustment for rifabutin is needed.
Rifampin	DOR	DOR AUC ↓ 88%	Contraindicated. After stopping rifampin, wait 4 weeks before initiating DOR.
	EFV	EFV AUC ↓ 26%	Do not use EFV 400 mg with rifampin. Maintain EFV dose at 600 mg once daily and monitor for virologic response.
	ETR	Significant ↓ ETR possible	Do not coadminister.
	NVP	NVP ↓ 20% to 58%	Do not coadminister.
	RPV IM	↓ RPV expected	Contraindicated.
	RPV PO	RPV AUC ↓ 80%	Contraindicated.
Rifapentine	DOR	DOR 100 mg Twice Daily plus Once-Weekly Rifapentine and Isoniazid Compared to DOR 100 mg Twice Daily Alone DOR AUC ↓ 29%, C_{min} ↓ 31%	Contraindicated. After stopping rifapentine, wait 4 weeks before initiating DOR.
	EFV	↔ EFV concentrations	No dose adjustment needed.
	ETR	↓ ETR possible	Do not coadminister.
	NVP	NVP C_{min} ↓ 27%	Do not coadminister.
	RPV IM, RPV PO	↓ RPV expected	Contraindicated.
Antibacterials—Macrolides			
Azithromycin	All NNRTIs	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	DOR	↔ clarithromycin expected ↑ DOR possible	Monitor for ARV tolerability if used in combination.
	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness, or consider alternative agent (e.g., azithromycin) for MAC prophylaxis and treatment.
	ETR	Clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31% NVP AUC ↑ 26%	Monitor for effectiveness, or consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RPV IM, RPV PO	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment. If coadministered, monitor for QTc prolongation.
Erythromycin	DOR	↑ DOR possible	Monitor for ARV tolerability if used in combination.
	EFV, ETR, NVP	↑ EFV, ETR, and NVP possible ↓ erythromycin possible	Monitor for ARV tolerability and antibiotic efficacy if used in combination.
	RPV IM, RPV PO	↑ RPV possible	Consider alternative macrolide (e.g., azithromycin). If coadministered, monitor for QTc prolongation.
Anticoagulants			
Apixaban	DOR, RPV IM, RPV PO	↔ apixaban expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ apixaban possible	Consider alternative ARV or anticoagulant therapy.
Dabigatran	All NNRTIs	↔ dabigatran expected	No dose adjustment needed.
Edoxaban	All NNRTIs	↔ edoxaban expected	No dose adjustment needed.
Rivaroxaban	DOR, RPV IM, RPV PO	↔ rivaroxaban expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ rivaroxaban possible	Consider alternative ARV or anticoagulant therapy.
Warfarin	DOR, RPV IM, RPV PO	↔ warfarin expected	No dose adjustment needed.
	EFV, ETR, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	DOR	↓ DOR possible	Contraindicated. After stopping anticonvulsant, wait 4 weeks before initiating DOR.
	EFV	Carbamazepine plus EFV Carbamazepine AUC ↓ 27% EFV AUC ↓ 36% Phenytoin plus EFV ↓ EFV ↑ or ↓ phenytoin possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor anticonvulsant and EFV concentrations.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	ETR	↓ anticonvulsant and ETR possible	Do not coadminister.
	NVP	↓ anticonvulsant and NVP possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor anticonvulsant and NVP concentrations and virologic response.
	RPV IM, RPV PO	↓ RPV possible	Contraindicated.
Eslicarbazepine	All NNRTIs	↓ NNRTI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor virologic response and consider monitoring plasma concentrations of ARVs.
Oxcarbazepine	DOR, RPV IM, RPV PO	↓ NNRTI possible	Contraindicated.
	EFV, ETR, NVP	↓ NNRTI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor virologic response and consider monitoring plasma concentrations of ARVs.
Ethosuximide, Lacosamide, Tiagabine, Zonisamide	DOR, RPV IM, RPV PO	↔ anticonvulsant expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ anticonvulsant possible	Monitor seizure control. Consider anticonvulsant therapeutic drug monitoring.
Lamotrigine	DOR, ETR, NVP, RPV IM, RPV PO	↔ lamotrigine expected	No dose adjustment needed.
	EFV	↓ lamotrigine possible	Monitor seizure control and plasma concentrations of lamotrigine.
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below.			
Bupropion	DOR, ETR, RPV IM, RPV PO	↔ bupropion expected	No dose adjustment needed.
	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
	NVP	↓ bupropion possible	
Citalopram, Escitalopram	DOR, RPV IM, RPV PO	↔ antidepressant expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antidepressant possible	Titrate antidepressant dose based on clinical response.
Fluoxetine, Fluvoxamine	All NNRTIs	↔ antidepressant expected	No dose adjustment needed.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Paroxetine	DOR, NVP, RPV IM, RPV PO	↔ paroxetine expected	No dose adjustment needed.
	EFV, ETR	↔ paroxetine expected	No dose adjustment needed.
Nefazodone	DOR, RPV IM, RPV PO	↑ NNRTI possible	No dose adjustment needed.
	EFV, ETR, NVP	↓ nefazodone expected ↑ NNRTI possible	Monitor antidepressant effect. Titrate dose as necessary based on clinical response.
Sertraline	DOR, RPV IM, RPV PO	↔ sertraline expected	No dose adjustment needed.
	EFV	Sertraline AUC ↓ 39%	Monitor the antidepressant effect. Titrate dose as necessary based on clinical response.
	ETR, NVP	↓ sertraline possible	
Trazodone	DOR, RPV IM, RPV PO	↔ trazodone expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ trazodone possible	Monitor for therapeutic effectiveness of trazodone and titrate dose as necessary.
Antipsychotics			
Aripiprazole	DOR, RPV IM, RPV PO	↔ aripiprazole expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ aripiprazole expected	Monitor for therapeutic effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks. Refer to aripiprazole prescribing information for dose recommendations.
Brexpiprazole	DOR, RPV IM, RPV PO	↔ brexpiprazole expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ brexpiprazole expected	Monitor for therapeutic effectiveness of antipsychotic. Consider doubling the usual dose of brexpiprazole and making further adjustments based on clinical response. Refer to brexpiprazole prescribing information.
Cariprazine	DOR, RPV IM, RPV PO	↔ cariprazine expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ cariprazine and ↑ or ↓ active metabolite possible	Do not coadminister.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Iloperidone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Lumateperone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Do not coadminister.
Lurasidone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Olanzapine	DOR, ETR, NVP, RPV IM, RPV PO	↔ olanzapine expected	No dose adjustment needed.
	EFV	↓ olanzapine possible	Monitor for therapeutic effectiveness of olanzapine.
Other Antipsychotics CYP3A4 substrates (e.g., clozapine, perphenazine, risperidone)	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Pimavanserin	DOR, RPV IM, RPV PO	↔ pimavanserin expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ pimavanserin expected	Do not coadminister.
Pimozide	DOR, RPV IM, RPV PO	↔ pimozide expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ pimozide possible	Monitor for therapeutic effectiveness of pimozide.
Quetiapine	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Ziprasidone	DOR, RPV IM, RPV PO	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Antifungals			
Fluconazole	DOR	↑ DOR possible	No dose adjustment needed.
	EFV	↔ fluconazole expected ↔ EFV AUC	No dose adjustment needed.
	ETR	ETR AUC ↑ 86%	No dose adjustment needed.
	NVP	NVP AUC ↑ 110%	Consider alternative ARV or antifungal agent. Increased risk of hepatotoxicity is possible with this combination.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Isavuconazole	DOR	↑ DOR possible	No dose adjustment needed.
	EFV, ETR, NVP	↓ isavuconazole possible	Monitor isavuconazole concentration and antifungal response. Dose adjustments for isavuconazole may be necessary.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Itraconazole	DOR	↑ DOR possible	No dose adjustment needed.
	EFV	Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 37% to 44%	Do not coadminister unless potential benefits outweigh the risks. Failure to achieve therapeutic itraconazole concentrations has been reported. If coadministration is necessary, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole concentration and antifungal response.
	NVP	Itraconazole AUC ↓ 61% ↑ NVP possible	Do not coadminister unless potential benefits outweigh the risks. If coadministration is necessary, monitor itraconazole concentration and adjust dose accordingly.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Posaconazole	DOR, ETR, NVP	↑ NNRTI possible	No dose adjustment needed.
	EFV	Posaconazole AUC ↓ 50% ↔ EFV AUC	Do not coadminister unless potential benefits outweigh the risks. If coadministration is necessary, monitor posaconazole concentration and adjust dose accordingly.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Voriconazole	DOR	↑ DOR possible	No dose adjustment needed.
	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	Contraindicated at standard doses. Adjust dose to voriconazole 400 mg twice daily plus EFV 300 mg daily.
	ETR	↔ voriconazole AUC ETR AUC ↑ 36%	No dose adjustment needed.
	NVP	↓ voriconazole possible ↑ NVP possible	Consider alternative ARV or antifungal agent. If coadministration is necessary, monitor ARV tolerability and antifungal response and/or voriconazole concentration.
	RPV IM, RPV PO	↑ RPV possible	No dose adjustment needed. If coadministered, consider monitoring for QTc prolongation.
Antimalarials			
Artemether/Lumefantrine	DOR, RPV IM, RPV PO	↔ antimalarial expected	No dose adjustment needed.
	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 30% to 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy.
	ETR	Artemether AUC ↓ 38% ↔ DHA AUC ↔ lumefantrine AUC ↔ ETR AUC	Clinical significance of the reduced antimalarial drug concentrations is unknown. If used in combination with ETR, monitor for antimalarial efficacy.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	NVP	Artemether AUC ↓ 67% to 72% DHA Study results are conflicting. DHA AUC ↓ 37% in one study, no difference in another. Lumefantrine Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in two studies, but ↑ 50% to 56% in another.	Clinical significance is unknown. If used in combination, monitor closely for antimalarial efficacy and lumefantrine toxicity.
Atovaquone/Proguanil	DOR, ETR, NVP, RPV IM, RPV PO	No data	Monitor for antimalarial efficacy.
	EFV	Atovaquone AUC ↓ 75% Proguanil AUC ↓ 43%	No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antiplatelets			
Clopidogrel	DOR, NVP, RPV IM, RPV PO	↔ clopidogrel expected	No dose adjustment needed.
	EFV, ETR	↓ activation of clopidogrel possible	Consider alternative ARV or antiplatelet. ETR may prevent metabolism of clopidogrel to its active metabolite.
Prasugrel	All NNRTIs	↔ prasugrel expected	No dose adjustment needed.
Ticagrelor	DOR, RPV IM, RPV PO	↔ ticagrelor expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ ticagrelor expected	Consider alternative ARV or anticoagulant therapy.
Vorapaxar	DOR, NVP, RPV IM, RPV PO	↔ vorapaxar expected	No dose adjustment needed.
	EFV, ETR	↓ vorapaxar expected	Insufficient data to make a dose recommendation.
Antipneumocystis and Anti-Toxoplasmosis Drugs			
Atovaquone (oral solution)	DOR, ETR, NVP, RPV IM, RPV PO	No data	Monitor for therapeutic effectiveness of atovaquone.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EFV	Atovaquone AUC ↓ 44% to 47%	Consider alternative ARV or agent for PCP or toxoplasmosis treatment or prophylaxis. If coadministration is necessary, monitor for therapeutic effectiveness of atovaquone.
Antivirals—Orthopoxviruses (Smallpox, Mpox)			
Brincidofovir	All NNRTIs	↔ brincidofovir expected	No dose adjustment needed.
Cidofovir	All NNRTIs	↔ cidofovir expected	No dose adjustment needed.
Tecovirimat	DOR, RPV PO	↓ DOR or RPV expected but not likely to be clinically relevant	No dose adjustment needed.
	EFV, ETR, NVP	↔ EFV, ETR, or NVP expected	No dose adjustment needed.
	RPV IM	↓ RPV expected but not likely to be clinically relevant	No dose adjustment needed. If there is a concern for suboptimal RPV exposure, seek expert consultation. Do not initiate CAB/RPV IM during and within 2 weeks after tecovirimat treatment. (Refer to Table 24d for interaction with CAB.)
Cardiac Medications			
Bosentan	DOR	↓ DOR possible	Consider alternative ARV or alternative to bosentan. If coadministration is necessary, monitor virologic response.
	EFV, ETR, NVP	↓ NNRTI possible ↓ bosentan possible	Consider alternative ARV or alternative to bosentan. If coadministration is necessary, monitor bosentan efficacy and virologic response.
	RPV IM, RPV PO	↓ RPV possible	Consider alternative ARV or alternative to bosentan. If coadministration is necessary, monitor virologic response.
Dihydropyridine CCBs	DOR, RPV IM, RPV PO	↔ CCBs expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem, Verapamil	DOR, RPV IM, RPV PO	↔ CCBs expected ↑ NNRTI possible	No dose adjustment needed.
	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	ETR, NVP	↓ diltiazem or verapamil possible	

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Dexamethasone	DOR, EFV, ETR, NVP	↓ NNRTI possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV IM, RPV PO	Significant ↓ RPV possible	Contraindicated with more than a single dose of dexamethasone.
Glucose-Lowering Agents			
Canagliflozin, Dapagliflozin, Empagliflozin, Sitagliptin	All NNRTIs	↔ antihyperglycemic expected	No dose adjustment needed.
Linagliptin, Saxagliptin	DOR, RPV IM, RPV PO	↔ antihyperglycemic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antihyperglycemic possible	Monitor glycemic control.
Metformin	DOR	↔ metformin AUC DOR AUC ↓ 26% and C_{max} ↓ 24%	No dose adjustment needed.
	EFV, ETR, NVP	↔ metformin expected	No dose adjustment needed.
	RPV IM	↔ metformin expected	No dose adjustment needed.
	RPV PO	↔ metformin AUC	No dose adjustment needed.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	DOR, RPV IM, RPV PO	No data	No dose adjustment needed.
	EFV, ETR, NVP	Daclatasvir 120 mg Once Daily plus EFV 600 mg Daily Compared to Daclatasvir 60 mg Alone Daclatasvir C_{min} ↓ 17% and AUC ↑ 37%	The recommended dose is daclatasvir 90 mg once daily.
Dasabuvir plus Paritaprevir/ Ombitasvir/RTV	DOR	↑ DOR possible	No dose adjustment needed.
	EFV	No data	Contraindicated.
	ETR, NVP	↓ DAAs possible	Do not coadminister.
	RPV IM	↑ RPV expected	Do not coadminister due to the potential for QTc prolongation with higher concentrations of RPV.
	RPV PO	RPV AUC ↑ 150% to 225%	Do not coadminister due to the potential for QTc prolongation with higher concentrations of RPV.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Elbasvir/Grazoprevir	DOR	↔ elbasvir and grazoprevir DOR AUC ↑ 56% and C_{min} ↑ 41%	No dose adjustment needed.
	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓ 83% ↔ EFV	Contraindicated.
	ETR, NVP	↓ elbasvir and grazoprevir expected	Do not coadminister.
	RPV IM	↔ elbasvir and grazoprevir expected ↔ RPV expected	No dose adjustment needed.
	RPV PO	↔ elbasvir and grazoprevir ↔ RPV AUC and C_{min}	No dose adjustment needed.
Glecaprevir/Pibrentasvir	DOR	↑ DOR expected	No dose adjustment needed.
	EFV	↓ glecaprevir and pibrentasvir expected	Do not coadminister.
	ETR	↓ glecaprevir and pibrentasvir possible	Do not coadminister.
	NVP	↓ glecaprevir and pibrentasvir possible	Consider alternative ARV or HCV regimen. If coadministration is necessary, monitor for HCV treatment efficacy.
	RPV IM	↔ glecaprevir and pibrentasvir expected ↑ RPV expected	No dose adjustment needed.
	RPV PO	↔ glecaprevir and pibrentasvir RPV AUC ↑ 84%	No dose adjustment needed.
Ledipasvir/Sofosbuvir	DOR	↔ ledipasvir and sofosbuvir ↔ DOR	No dose adjustment needed.
	EFV	Ledipasvir AUC, C_{min}, and C_{max} ↓ 34% ↔ sofosbuvir	
	ETR, NVP	No significant effect expected	
	RPV IM	↔ ledipasvir, sofosbuvir, and RPV expected	
	RPV PO	↔ ledipasvir and sofosbuvir ↔ RPV	

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sofosbuvir/Velpatasvir	DOR, RPV IM, RPV PO	No significant effect expected	No dose adjustment needed.
	EFV	Velpatasvir AUC ↓ 43%, C_{max} ↓ 37%, and C_{min} ↓ 47%	Do not coadminister.
	ETR, NVP	↓ velpatasvir expected	Do not coadminister.
Sofosbuvir/Velpatasvir/ Voxilaprevir	DOR, RPV IM, RPV PO	No significant effect expected	No dose adjustment needed.
	EFV	Velpatasvir AUC ↓ 43%, C_{max} ↓ 37%, and C_{min} ↓47% ↓ voxilaprevir expected	Do not coadminister.
	ETR, NVP	↓ voxilaprevir expected ↓ velpatasvir expected	Do not coadminister.
Herbal Products			
St. John's Wort	DOR	↓ DOR expected	Contraindicated. After stopping St. John's Wort, wait 4 weeks before initiating DOR.
	EFV, ETR, NVP	↓ EFV, ETR, and NVP expected	Do not coadminister.
	RPV IM, RPV PO	↓ RPV expected	Contraindicated.
Hormonal Therapies			
Contraceptives—Injectable Depot MPA	DOR, ETR, RPV IM, RPV PO	↔ MPA expected	No dose adjustment needed.
	EFV, NVP	↔ MPA	No dose adjustment needed.
Contraceptives—Oral	DOR	↔ ethinyl estradiol ↔ levonorgestrel	No dose adjustment needed.
	EFV	↔ ethinyl estradiol Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 61% Levonorgestrel (metabolite of oral norgestimate) AUC ↓ 83% Norelgestromin (metabolite of oral norgestimate) AUC ↓ 64%	When Used for Contraception Use alternative ARV or contraceptive methods. When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation) Monitor for clinical effectiveness of hormonal therapy.
	ETR	Ethinyl estradiol AUC ↑ 22% ↔ norethindrone	No dose adjustment needed.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	NVP	Ethinyl estradiol AUC ↓ 29% and C_{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 22%	No dose adjustment needed based on clinical data that demonstrated no change in effectiveness.
	RPV IM	↔ ethinyl estradiol expected ↔ norethindrone expected	No dose adjustment needed.
	RPV PO	↔ ethinyl estradiol ↔ norethindrone	No dose adjustment needed.
Contraceptives—Subdermal Implant Etonogestrel	DOR, RPV IM, RPV PO	↔ etonogestrel expected	No dose adjustment needed.
	EFV	Etonogestrel AUC ↓ 63% to 82%	Use alternative ARV or contraceptive methods.
	ETR	↓ etonogestrel possible	No data available to make dose recommendation.
	NVP	↔ etonogestrel	No dose adjustment needed.
Contraceptives—Subdermal Implant Levonorgestrel	DOR, RPV IM, RPV PO	↔ levonorgestrel expected	No dose adjustment needed.
	EFV	Levonorgestrel AUC ↓ 42% to 47%	Use alternative ARV or contraceptive methods. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.
	ETR	↓ levonorgestrel possible	No data available to make dose recommendation.
	NVP	Levonorgestrel AUC ↑ 35%	No dose adjustment needed.
Contraceptives—Transdermal Ethinyl Estradiol/ Norelgestromin	DOR, RPV IM, RPV PO	↔ ethinyl estradiol or norelgestromin expected	No dose adjustment needed.
	EFV	↓ ethinyl estradiol or norelgestromin expected	No data available to make dose recommendation.
	ETR, NVP	↓ ethinyl estradiol or norelgestromin possible	No data available to make dose recommendation.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Contraceptives—Vaginal Ring Etonogestrel/Ethinyl Estradiol	DOR, RPV IM, RPV PO	↔ etonogestrel and ethinyl estradiol expected	No dose adjustment needed.
	EFV	Ethinyl estradiol (intravaginal ring) AUC ↓ 56% Etonogestrel (intravaginal ring) AUC ↓ 81%	Consider alternative ARV or contraceptive method.
	ETR, NVP	↓ etonogestrel and ethinyl estradiol possible	No data available to make dose recommendation.
Contraceptives—Vaginal Ring Segesterone/Ethinyl Estradiol	DOR, RPV IM, RPV PO	↔ segesterone and ethinyl estradiol expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ segesterone and ethinyl estradiol possible	No data available to make dose recommendation.
Emergency Contraceptives Levonorgestrel (oral)	DOR, RPV IM, RPV PO	↔ levonorgestrel expected	No dose adjustment needed.
	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
	NVP, ETR	↓ levonorgestrel possible	No data available to make dose recommendation.
Gender-Affirming Therapy	DOR, RPV IM, RPV PO	↔ hormonal concentrations expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ estradiol possible ↓ cyproterone and progestogens possible ↔ goserelin, leuprolide acetate, and spironolactone expected ↓ dutasteride and finasteride possible	Monitor feminizing effects of estrogen and antiandrogen therapy. Titrate dose as necessary to achieve therapeutic goals.
	EFV, ETR, NVP	↓ testosterone possible	Monitor masculinizing effects of testosterone. Titrate testosterone dose as necessary to achieve therapeutic goals.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Menopausal Replacement Therapy	DOR, RPV IM, RPV PO	↔ hormonal concentrations expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic) ↓ medroxyprogesterone possible ↓ micronized progesterone possible ↓ drospirenone possible See Contraceptives—Oral above for other progestin-NNRTI interactions	Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief.
Immunosuppressants			
Cyclosporine	DOR, RPV IM, RPV PO	↔ cyclosporine expected ↑ NNRTI possible	No dose adjustment needed.
	EFV, ETR, NVP	↓ cyclosporine possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Everolimus, Sirolimus, Tacrolimus	DOR, RPV IM, RPV PO	↔ immunosuppressant expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	DOR	↔ atorvastatin AUC	No dose adjustment needed.
	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	NVP	↓ atorvastatin possible	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	RPV IM	↔ atorvastatin expected	No dose adjustment needed.
	RPV PO	↔ atorvastatin AUC	No dose adjustment needed.
Fluvastatin	DOR, NVP, RPV IM, RPV PO	↔ fluvastatin expected	No dose adjustment needed.
	EFV, ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lovastatin, Simvastatin	DOR, RPV IM, RPV PO	↔ lovastatin and simvastatin expected	No dose adjustment needed.
	EFV	Simvastatin AUC ↓ 60% to 68% Simvastatin active metabolite AUC ↓ 60%	Adjust simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Pitavastatin	DOR, ETR, NVP, RPV IM, RPV PO	↔ pitavastatin expected	No dose adjustment needed.
	EFV	↔ pitavastatin AUC	No dose adjustment needed.
Pravastatin	DOR, NVP, RPV IM, RPV PO	↔ pravastatin expected	No dose adjustment needed.
	EFV	Pravastatin AUC ↓ 44%	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
	ETR	↓ pravastatin possible	
Rosuvastatin	DOR, EFV, ETR, NVP, RPV IM, RPV PO	↔ rosuvastatin expected	No dose adjustment needed.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual or buccal	DOR, RPV IM, RPV PO	↔ buprenorphine expected	No dose adjustment needed.
	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine (active metabolite) AUC ↓ 71%	No dose adjustment needed, monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment needed.
	NVP	No significant effect	No dose adjustment needed.
Buprenorphine Implant	DOR, RPV IM, RPV PO	↔ buprenorphine expected	No dose adjustment needed.
	EFV, ETR, NVP	No data	Clinical monitoring is recommended when NNRTI is initiated after insertion of buprenorphine implant.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lofexidine	DOR, EFV, ETR, NVP, RPV IM, RPV PO	↔ lofexidine expected	No dose adjustment needed.
Methadone	DOR	↔ methadone AUC DOR AUC ↓ 26%	No dose adjustment needed.
	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; monitor and increase methadone dose as necessary.
	ETR	↔ methadone AUC	No dose adjustment needed.
	NVP	Methadone AUC ↓ 37% to 51% ↔ NVP	Opioid withdrawal common; monitor and increase methadone dose as necessary.
	RPV IM	↓ methadone AUC expected	No dose adjustment needed, but monitor for withdrawal symptoms.
	RPV PO	R-methadone[a] AUC ↓ 16%	No dose adjustment needed, but monitor for withdrawal symptoms.
PDE5 Inhibitors			
Sildenafil	DOR	↔ sildenafil expected	No dose adjustment needed.
	EFV, NVP	↓ sildenafil possible	May need to titrate sildenafil dose based on clinical effect.
	ETR	Sildenafil AUC ↓ 57%	May need to titrate sildenafil dose based on clinical effect.
	RPV IM	↔ sildenafil expected	No dose adjustment needed.
	RPV PO	↔ sildenafil AUC and C_{max}	No dose adjustment needed.
Tadalafil	DOR, RPV IM, RPV PO	↔ tadalafil expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ tadalafil possible	May need to titrate tadalafil dose based on clinical effect.
Avanafil, Vardenafil	DOR, RPV IM, RPV PO	↔ avanafil or vardenafil expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ avanafil or vardenafil possible	May need to increase PDE5 inhibitor dose based on clinical effect.
Sedative/Hypnotics			
Alprazolam, Triazolam	DOR, RPV IM, RPV PO	↔ alprazolam or triazolam expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ alprazolam or triazolam possible	Monitor for therapeutic effectiveness of benzodiazepine.

Table 24b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Diazepam	DOR, RPV IM, RPV PO	↔ diazepam expected	No dose adjustment needed.
	EFV, NVP	↓ diazepam possible	Monitor for therapeutic effectiveness of diazepam.
	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary. Monitor for diazepam toxicity.
Lorazepam	DOR, ETR, NVP, RPV IM, RPV PO	↔ lorazepam expected	No dose adjustment needed.
	EFV	↔ lorazepam AUC	No dose adjustment needed.
Midazolam	DOR	↔ midazolam AUC	No dose adjustment needed.
	EFV	↑ or ↓ midazolam possible	Monitor for therapeutic effectiveness and toxicity of midazolam.
	ETR	Midazolam AUC ↓ 31% Midazolam active metabolite C_{max} ↑ 57%	Monitor for therapeutic effectiveness of midazolam.
	NVP	↓ midazolam possible	Monitor for therapeutic effectiveness of midazolam.
	RPV IM, RPV PO	↔ midazolam expected	No dose adjustment needed.

[a] R-methadone is the active form of methadone.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: ARV = antiretroviral; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CAB = cabotegravir; CCB = calcium channel blocker; DAA = direct-acting antiviral; DHA = dihydroartemisinin; DOR = doravirine; EFV = efavirenz; ETR = etravirine; HCV = hepatitis C virus; IM = intramuscular; INR = international normalized ratio; isoniazid = isonicotinic acid hydrazide; MAC = *Mycobacterium avium* complex; MPA = medroxyprogesterone acetate; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PCP = *Pneumocystis jirovecii* pneumonia; PDE5 = phosphodiesterase type 5; PI/r = protease inhibitor/ritonavir; PO = orally; QTc = QT corrected for heart rate; RPV = rilpivirine; RTV = ritonavir.

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Updated: September 01, 2022
Reviewed: September 01, 2022

This table provides information on the known or predicted interactions between nucleoside reverse transcriptase inhibitors (NRTIs) and non-antiretroviral drugs.

Recommendations for managing a particular drug interaction may differ depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Interactions associated with zidovudine are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions between these NRTIs and other drugs.

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials			
Rifabutin	TAF	↓ TAF possible	Do not coadminister unless benefits outweigh risks. If coadministered, monitor for virologic response.
	TDF	↔ AUC TFV	No dose adjustment needed.
Rifampin	TAF	TAF With Rifampin Compared With TDF Alone • TFV-DP AUC ↑ 4.2-fold TAF With Rifampin Compared With TAF Alone • TAF AUC ↓ 55% • TFV-DP AUC ↓ 36% TAF 25 mg Twice Daily With Rifampin Compared With TAF Once Daily Alone • TAF AUC ↓ 14% • TFV-DP AUC ↓ 24%	Do not coadminister unless benefits outweigh risks. Intracellular TFV-DP levels are higher when TAF is coadministered with rifampin than when TDF is administered alone, but clinical outcomes have not been studied. If coadministered, monitor virologic response.
	TDF	↔ AUC TFV	No dose adjustment needed.

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifapentine	TAF	↓ TAF possible	Do not coadminister unless benefits outweigh risks. If coadministered, monitor for virologic response.
	TDF	↔ AUC TFV	No dose adjustment needed.
Antivirals – Orthopoxviruses (Smallpox, Mpox)			
Brincidofovir	All NRTIs	↔ brincidofovir expected	No dose adjustment needed.
Cidofovir	ABC, 3TC, FTC, TAF	↔ cidofovir expected	No dose adjustment needed.
	TDF	↑ TDF and cidofovir possible	Potential for renal toxicity when TDF is given with a nephrotoxic agent, such as cidofovir. If concomitant use is necessary, closely monitor renal function.
Tecovirimat	All NRTIs	↔ tecovirimat expected	No dose adjustment needed.
Cytomegalovirus and Hepatitis B Antivirals			
Adefovir	TAF, TDF	No data	Do not coadminister. Serum concentrations of TDF and/or other renally eliminated drugs may increase.
Ganciclovir, Valganciclovir	TAF, TDF	No data	Serum concentrations of ganciclovir and/or TFV may increase. Monitor for dose-related toxicities.
Hormonal Therapies			
17-β-estradiol	FTC	FTC AUC ↓ 14% to 24%	No dose adjustment needed.
	TDF	TFV AUC ↓ 12% to 27%	No dose adjustment needed.
Other hormones used for contraception, gender affirming therapy, or menopausal replacement therapy	All NRTIs	No change expected.	No dose adjustment needed.
Hepatitis C Antiviral Agents			
Glecaprevir/Pibrentasvir	TAF	↔ TFV AUC	No dose adjustment needed.
	TDF	TFV AUC ↑ 29%	No dose adjustment needed.

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Ledipasvir/Sofosbuvir	TAF	TFV AUC ↑ 27%	No dose adjustment needed.
	TDF	Ledipasvir ↑ TFV AUC 35% to 98% when TDF is given with various PIs and NNRTIs. Ledipasvir ↑ TFV C_{min} 55% to 80% when TDF is given with various PIs, NNRTIs, or INSTIs. Further ↑ TFV AUC and C_{max} possible when TDF, ledipasvir/sofosbuvir, and PIs are coadministered.	Do not coadminister with EVG/c, TDF, or FTC. If TDF is used, monitor for TDF toxicities. Consider using TAF in patients at risk of TDF-associated adverse events. Consider using TAF or alternative HCV therapy in patients on TDF plus a PI/r or PI/c. The safety of increased TFV exposure with this combination has not been established.
Ribavirin	TDF	Ribavirin With Sofosbuvir 400 mg • ↔ TFV AUC	No dose adjustment needed.
Sofosbuvir/Velpatasvir	TAF	↔ TFV expected	No dose adjustment needed.
	TDF	TFV C_{max} ↑ 44% to 46% and AUC ↑ 40% when coadministered with various ARV combinations.	If TDF is used in these patients, monitor for TDF-related toxicities. Consider using TAF in patients at risk of TDF-related adverse events.
Sofosbuvir/Velpatasvir/ Voxilaprevir	TAF	↔ TAF expected	No dose adjustment needed.
	TDF	TFV C_{max} ↑ 48% and AUC ↑ 39% when coadministered with various ARV combinations.	If TDF is used in these patients, monitor for TDF-related toxicities. Consider using TAF in patients at risk of TDF-related adverse events.
INSTIs			
DTG	TAF	↔ TAF AUC	No dose adjustment needed.
	TDF	↔ TDF AUC ↔ DTG AUC	No dose adjustment needed.
RAL	TDF	RAL AUC ↑ 49%	No dose adjustment needed.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine	3TC, TDF	↔ 3TC, TDF, and buprenorphine	No dose adjustment needed.
	TAF	↔ TAF expected	No dose adjustment needed.
Methadone	ABC	Methadone clearance ↑ 22%	No dose adjustment needed.

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Other Drugs			
Anticonvulsants Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	TAF	With Carbamazepine • TAF AUC ↓ 55% ↓ TAF possible with other anticonvulsants	Do not coadminister.
Riociguat	ABC	Riociguat AUC ↑ 200%	If coadministered, initiate riociguat at 0.5 mg three times daily and monitor for riociguat-related adverse effects (e.g., hypotension).
St. John's Wort	TAF	↓ TAF possible	Do not coadminister.
PIs for Treatment of HIV			
ATV (Unboosted), ATV/c, ATV/r	TAF	TAF 10 mg With ATV/r • TAF AUC ↑ 91% TAF 10 mg With ATV/c • TAF AUC ↑ 75%	No dose adjustment needed (use TAF 25 mg).
	TDF	With ATV (Unboosted) • ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) • TFV AUC ↑ 24% to 37%	Do not coadminister unboosted ATV with TDF. Use ATV 300 mg plus (RTV 100 mg or COBI 150 mg) daily when coadministering TDF 300 mg daily. If using TDF and an H2 receptor antagonist in an ART-experienced patient, use ATV 400 mg plus (RTV 100 mg or COBI 150 mg) daily Monitor for TDF-associated toxicities.
DRV/c	TAF	TAF 25 mg With DRV/c • ↔ TAF	No dose adjustment needed.
	TDF	TFV ↑ possible	Monitor for TDF-associated toxicities.
DRV/r	TAF	TAF 10 mg With DRV/r • ↔ TAF AUC	No dose adjustment needed.
	TDF	TFV AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance is unknown. If coadministered, monitor for TDF-associated toxicities.

Table 24c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
LPV/r	TAF	TAF 10 mg With LPV/r • TAF AUC ↑ 47%	No dose adjustment needed.
	TDF	↔ LPV/r AUC TFV AUC ↑ 32%	Clinical significance is unknown. If coadministered, monitor for TDF-associated toxicities.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI = cobicistat; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Updated: September 01, 2022
Reviewed: September 01, 2022

This table provides information on the known or predicted interactions between integrase strand transfer inhibitors (INSTIs) (bictegravir [BIC], dolutegravir [DTG], elvitegravir [EVG], or raltegravir [RAL]) and non-antiretroviral (ARV) drugs. EVG is always coadministered with cobicistat. Cabotegravir (CAB) intramuscular (IM) plus rilpivirine (RPV) IM are co-packaged into a single product and are coadministered as a complete regimen; therefore, the dosing recommendations and clinical comments reflect the combination of CAB IM and RPV IM treatments. Drug interaction studies were not conducted with either CAB IM or RPV IM. Drug interaction studies with oral CAB and RPV were leveraged to make the dosing recommendations for CAB IM and RPV IM. For information regarding interactions between INSTIs and other ARV drugs, including dosing recommendations, refer to Tables 24c, 24e, 24f, and 25b.

Recommendations for managing a particular drug interaction may differ, depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Al, Mg, +/– Ca-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe and Ca supplements, multivitamins).	BIC	Al/Mg Hydroxide Antacid • ↔ BIC AUC if antacid is administered 2 hours after BIC and under fasting conditions • BIC AUC ↓ 52% if antacid is administered 2 hours before BIC • BIC AUC ↓ 47% to 79% if administered simultaneously with antacid $CaCO_3$ Antacid • ↔ BIC AUC if administered with food • BIC AUC ↓ 33% if administered under fasting conditions	With Antacids That Contain Al/Mg • Administer antacids that contain Al/Mg at least 2 hours after or 6 hours before BIC. With Antacids That Contain Ca • Administer BIC and antacids that contain Ca together with food. • Do not coadminister BIC simultaneously with antacids that contain Ca on an empty stomach.
	CAB PO	CAB PO ↓ expected	With Antacids That Contain Polyvalent Cations (Al, Mg, or Ca) • Administer antacid products at least 2 hours before or 4 hours after taking CAB PO.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	CAB IM	↔ CAB IM expected	No dose adjustment needed.
	DTG	DTG AUC ↓ 74% if administered simultaneously with antacid DTG AUC ↓ 26% if administered 2 hours before antacid	Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations.
	EVG/c	EVG AUC ↓ 40% to 50% if administered simultaneously with antacid EVG AUC ↓ 15% to 20% if administered 2 hours before or after antacid; ↔ with a 4-hour interval	Separate EVG/c and antacid administration by more than 2 hours.
	RAL	Al/Mg Hydroxide Antacid • RAL C_{min} ↓ 49% to 63% $CaCO_3$ Antacid • RAL 400 mg twice daily: C_{min} ↓ 32% • RAL 1,200 mg once daily: C_{min} ↓ 48% to 57%	Do not coadminister RAL and Al/Mg hydroxide antacids. Use alternative acid-reducing agent. With $CaCO_3$ Antacids • RAL 1,200 mg once daily: Do not coadminister. • RAL 400 mg twice daily: No dose adjustment or separation needed.
H2-Receptor Antagonists	BIC, CAB (PO and IM), DTG, EVG/c	↔ INSTI	No dose adjustment needed.
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment needed.
Proton Pump Inhibitors	BIC, CAB (PO and IM), DTG, EVG/c	↔ INSTI	No dose adjustment needed.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment needed.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, CAB (PO and IM), DTG, RAL	↔ alfuzosin expected	No dose adjustment needed.
	EVG/c	↑ alfuzosin expected	Contraindicated.
Doxazosin	BIC, CAB (PO and IM), DTG, RAL	↔ doxazosin expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose. Titrate based on doxazosin efficacy and adverse events. Doxazosin dose reduction may be needed.
Tamsulosin	BIC, CAB (PO and IM), DTG, RAL	↔ tamsulosin expected	No dose adjustment needed.
	EVG/c	↑ tamsulosin expected	Do not coadminister unless the benefits outweigh the risks. If coadministered, monitor for tamsulosin-related adverse events.
Terazosin	BIC, CAB (PO and IM), DTG, RAL	↔ terazosin expected	No dose adjustment needed.
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose. Titrate based on terazosin efficacy and adverse events. Terazosin dose reduction may be necessary.
Silodosin	BIC, CAB (PO and IM), DTG, RAL	↔ silodosin expected	No dose adjustment needed.
	EVG/c	↑ silodosin expected	Contraindicated.
Antibacterials - Antimycobacterials			
Rifabutin	BIC	Rifabutin 300 mg Once Daily • BIC AUC ↓ 38% and C_{min} ↓ 56%	Do not coadminister.
	CAB PO	CAB PO AUC ↓ 23% and C_{min} ↓ 26% ↔ rifabutin	No dose adjustment needed.
	CAB IM	↓ CAB IM and RPV expected ↔ rifabutin expected	Contraindicated due to ↓ RPV, which is co-packaged and coadministered with CAB IM.
	DTG	Rifabutin 300 mg Once Daily • ↔ DTG AUC and C_{min} ↓ 30%	No dose adjustment needed.
	EVG/c	Rifabutin 150 mg Every Other Day With EVG/c Once Daily Compared to Rifabutin 300 mg Once Daily Alone • ↔ rifabutin AUC • 25-O-desacetyl-rifabutin AUC ↑ 625% • EVG AUC ↓ 21% and C_{min} ↓ 67%	Do not coadminister.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dose adjustment needed.
Rifampin	BIC	BIC AUC ↓ 75%	Contraindicated.
	CAB PO	CAB PO AUC ↓ 59% and C_{min} ↓ 50%	Contraindicated.
	CAB IM	CAB IM ↓ expected	Contraindicated.
	DTG	Rifampin With DTG 50 mg Twice Daily Compared to DTG 50 mg Twice Daily Alone • DTG AUC ↓ 54% and C_{min} ↓ 72% Rifampin With DTG 50 mg Twice Daily Compared to DTG 50 mg Once Daily Alone • DTG AUC ↑ 33% and C_{min} ↑ 22%	Use DTG 50 mg twice daily (instead of DTG 50 mg once daily) in patients without suspected or documented INSTI-associated resistance mutations. Consider an alternative to rifampin, such as rifabutin, in patients with certain suspected or documented INSTI-associated resistance mutations.
	EVG/c	Significant ↓ EVG and COBI expected	Contraindicated.
	RAL	RAL 400 mg • RAL AUC ↓ 40% and C_{min} ↓ 61% Rifampin With RAL 800 mg Twice Daily Compared to RAL 400 mg Twice Daily Alone • RAL AUC ↑ 27% and C_{min} ↓ 53%	Use RAL 800 mg twice daily instead of 400 mg twice daily. Do not coadminister RAL 1,200 mg once daily with rifampin. Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	BIC, EVG/c	Significant ↓ BIC, EVG, and COBI expected	Do not coadminister.
	CAB (PO and IM)	Significant ↓ CAB (PO and IM) expected	Contraindicated.
	DTG	Rifapentine 900 mg Once Weekly • DTG AUC ↓ 26% and C_{min} ↓ 47%	With once-weekly rifapentine, DTG 50 mg daily may be used in patients with viral suppression on daily DTG. Monitor for virologic efficacy. Do not coadminister in patients who require twice-daily DTG. Do not coadminister DTG with once-daily rifapentine.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	RAL	Rifapentine 900 mg Once Weekly • RAL AUC ↑ 71% and C_{min} ↓ 12% Rifapentine 600 mg Once Daily • RAL C_{min} ↓ 41%	For once-weekly rifapentine and RAL 400 mg twice daily, no dose adjustment is needed. Do not coadminister with once-daily rifapentine.
Antibacterials - Macrolides			
Azithromycin	All INSTIs	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	BIC	↑ BIC possible	No dose adjustment needed.
	CAB (PO and IM), DTG, RAL	↔ clarithromycin expected	No dose adjustment needed.
	EVG/c	↑ clarithromycin expected ↑ COBI possible	Reduce clarithromycin dose by 50% in patients with CrCl 50 to 60 mL/min. Do not coadminister in patients with CrCl <50 mL/min. Consider alternative ARV or use azithromycin.
Erythromycin	BIC	↑ BIC possible	No dose adjustment needed.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ erythromycin expected	No dose adjustment needed.
	EVG/c	↑ erythromycin expected ↑ COBI possible	No data available for dose recommendation. Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	BIC, CAB (PO and IM), DTG, RAL	↔ apixaban expected	No dose adjustment needed.
	EVG/c	↑ apixaban expected	Do not coadminister in patients who require apixaban 2.5 mg twice daily. Reduce apixaban dose by 50% in patients who require apixaban 5 mg or 10 mg twice daily.
Dabigatran	BIC, CAB (PO and IM), DTG, RAL	↔ dabigatran expected	No dose adjustment needed.
	EVG/c	↑ dabigatran expected With COBI 150 mg Alone • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instructions when using dabigatran concomitantly with P-glycoprotein inhibitors.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Edoxaban	BIC, CAB (PO and IM), DTG, RAL	↔ edoxaban expected	No dose adjustment needed.
	EVG/c	↑ edoxaban expected	Stroke Prevention in Nonvalvular Atrial Fibrillation • No dose adjustment needed. Deep Venous Thrombosis and Pulmonary Embolism • Administer edoxaban 30 mg once daily.
Rivaroxaban	BIC, CAB (PO and IM), DTG, RAL	↔ rivaroxaban expected	No dose adjustment needed.
	EVG/c	↑ rivaroxaban expected	Do not coadminister.
Warfarin	BIC, CAB (PO and IM), DTG, RAL	↔ warfarin expected	No dose adjustment needed.
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	BIC	↓ BIC possible	Do not coadminister.
	CAB (PO and IM)	↓ CAB expected	Contraindicated.
	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg twice daily in ART-naive or ART-experienced (but INSTI-naive) patients. Do not coadminister in INSTI-experienced patients with known or suspected INSTI resistance.
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	Contraindicated.
	RAL	↓ or ↔ RAL possible	Do not coadminister.
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider alternative ARV or anticonvulsant.
Ethosuximide	BIC, CAB (PO and IM), DTG, RAL	↔ ethosuximide expected	No dose adjustment needed.
	EVG/c	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lamotrigine	BIC, CAB (PO and IM), DTG, RAL	↔ lamotrigine expected	No dose adjustment needed.
	EVG/c	No data	Monitor anticonvulsant concentrations and adjust dose accordingly.
Oxcarbazepine	BIC, DTG	↓ BIC and DTG possible	Do not coadminister.
	CAB (PO and IM)	↓ CAB expected	Contraindicated.
	EVG/c, RAL	↓ EVG/c and RAL possible	Consider alternative ARV or anticonvulsant.
Phenobarbital, Phenytoin	BIC, DTG, RAL	↓ BIC and DTG possible ↓ or ↔ RAL possible	Do not coadminister.
	CAB (PO and IM), EVG/c	↓ CAB and EVG/c expected	Contraindicated.
Valproic Acid	All INSTIs	No data	Monitor valproic acid concentration and virologic response.
Antidepressants, Anxiolytics, and Antipsychotics Also see the Sedative/Hypnotics section below			
Bupropion	BIC, CAB (PO and IM), DTG, RAL	↔ bupropion expected	No dose adjustment needed.
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, CAB (PO and IM), DTG, RAL	↔ buspirone expected	No dose adjustment needed.
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Buspirone dose reduction may be needed.
Nefazodone	BIC, CAB (PO and IM), DTG, RAL	↔ nefazodone expected	No dose adjustment needed.
	EVG/c	↑ nefazodone expected	Consider alternative ARV or antidepressant.
Trazodone	BIC, CAB (PO and IM), DTG, RAL	↔ trazodone expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Tricyclic Antidepressants Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	BIC, CAB (PO and IM), DTG, RAL	↔ TCA expected	No dose adjustment needed.
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA. Titrate dose carefully based on antidepressant response and/or drug concentrations.
Selective Serotonin Reuptake Inhibitors Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	EVG/c	↔ sertraline	No dose adjustment needed.
	EVG/c	↑ other SSRIs possible	Initiate with lowest dose of SSRI. Titrate dose carefully based on antidepressant response.
	BIC, CAB (PO and IM), DTG, RAL	↔ SSRI expected	No dose adjustment needed.
Antipsychotics			
Aripiprazole	BIC, CAB (PO and IM), DTG, RAL	↔ aripiprazole expected	No dose adjustment needed.
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate based on aripiprazole efficacy and adverse events. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Brexpiprazole	BIC, CAB (PO and IM), DTG, RAL	↔ brexpiprazole expected	No dose adjustment needed.
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on brexpiprazole efficacy and adverse events. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Cariprazine	BIC, CAB (PO and IM), DTG, RAL	↔ cariprazine expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ cariprazine expected	Starting Cariprazine in a Patient Who Is Already Receiving EVG/c • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum of cariprazine 3 mg daily. If EVG/c is withdrawn, cariprazine dose may need to be increased. Starting EVG/c in a Patient Who Is Already Receiving Cariprazine • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce the dose by half. For patients receiving cariprazine 4.5 mg daily, reduce dose to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients receiving cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If EVG/c is withdrawn, cariprazine dose may need to be increased.
Iloperidone	BIC, CAB (PO and IM), DTG, RAL	↔ iloperidone expected	No dose adjustment needed.
	EVG/c	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lumateperone	BIC, CAB (PO and IM), DTG, RAL	↔ lumateperone expected	No dose adjustment needed.
	EVG/c	↑ lumateperone expected	Do not coadminister.
Lurasidone	BIC, CAB (PO and IM), DTG, RAL	↔ lurasidone expected	No dose adjustment needed.
	EVG/c	↑ lurasidone expected	Contraindicated.
Olanzapine	All INSTIs	↔ olanzapine expected	No dose adjustment needed.
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., perphenazine, risperidone, thioridazine)	EVG/c	↑ antipsychotic possible	Initiate antipsychotic at a low dose. Antipsychotic dose reduction may be needed.
Pimavanserin	BIC, CAB (PO and IM), DTG, RAL	↔ pimavanserin expected	No dose adjustment needed.
	EVG/c	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg.
Pimozide	BIC, CAB (PO and IM), DTG, RAL	↔ pimozide expected	No dose adjustment needed.
	EVG/c	↑ pimozide expected	Contraindicated.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Quetiapine	BIC, CAB (PO and IM), DTG, RAL	↔ quetiapine expected	No dose adjustment needed.
	EVG/c	↑ quetiapine AUC expected	Starting Quetiapine in a Patient Receiving EVG/c • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse events. Starting EVG/c in a Patient Receiving a Stable Dose of Quetiapine • Reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine efficacy and adverse events.
Ziprasidone	BIC, CAB (PO and IM), DTG, RAL	↔ ziprasidone expected	No dose adjustment needed.
	EVG/c	↑ ziprasidone possible	Monitor for ziprasidone-related adverse events.
Antifungals			
Isavuconazole	BIC, CAB (PO and IM), DTG, RAL	↑ INSTI possible	No dose adjustment needed.
	EVG/c	↑ isavuconazole expected ↑ or ↓ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assessing virologic response.
Itraconazole	BIC	↑ BIC expected	No dose adjustment needed.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ itraconazole expected	No dose adjustment needed.
	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole concentrations to guide dose adjustments. Do not coadminister with high itraconazole doses (>200 mg/day) unless guided by itraconazole concentrations.
Posaconazole	BIC	↑ BIC expected	No dose adjustment needed.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ posaconazole expected	No dose adjustment needed.
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment needed.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ voriconazole expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	Do not coadminister voriconazole and COBI, unless the benefit outweighs the risk. If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antihyperglycemics			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for adverse events of metformin.
	DTG	DTG 50 mg Once Daily plus Metformin 500 mg Twice Daily • Metformin AUC ↑ 79% and C_{max} ↑ 66% DTG 50 mg Twice Daily plus Metformin 500 mg Twice Daily • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at the lowest dose and titrate based on glycemic control. Monitor for adverse events of metformin. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse events of metformin.
	CAB (PO and IM), RAL	↔ metformin expected	No dose adjustment needed.
Saxagliptin	BIC, CAB (PO and IM), DTG, RAL	↔ saxagliptin expected	No dose adjustment needed.
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/ Saxagliptin	BIC, CAB (PO and IM), DTG, RAL	↔ dapagliflozin or saxagliptin expected	No dose adjustment needed.
	EVG/c	↑ saxagliptin expected	Do not coadminister. Dapagliflozin is available only as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination is not recommended.
Antiplatelets			
Clopidogrel	BIC, CAB (PO and IM), DTG, RAL	↔ clopidogrel expected	No dose adjustment needed.
	EVG/c	↓ clopidogrel active metabolite, with impaired platelet inhibition expected	Do not coadminister.
Prasugrel	BIC, CAB (PO and IM), DTG, RAL	↔ prasugrel expected	No dose adjustment needed.
	EVG/c	↓ prasugrel active metabolite, with no impairment of platelet inhibition expected	No dose adjustment needed.

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Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Ticagrelor	BIC, CAB (PO and IM), DTG, RAL	↔ ticagrelor expected	No dose adjustment needed.
	EVG/c	↑ ticagrelor expected	Do not coadminister.
Vorapaxar	BIC, CAB (PO and IM) DTG, RAL	↔ vorapaxar expected	No dose adjustment needed.
	EVG/c	↑ vorapaxar expected	Do not coadminister.
Antivirals—Orthopoxviruses (Smallpox, Mpox)			
Brincidofovir	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected	No dose adjustment needed.
	EVG/c	↑ brincidofovir possible ↑ EVG possible	Administer EVG/c dose at least 3 hours after administering brincidofovir and monitor for brincidofovir-related adverse events (i.e., elevations in ALT/AST and bilirubin and GI adverse events).
Cidofovir	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ cidofovir expected	No dose adjustment needed.
Tecovirimat	CAB (IM)	↔ CAB expected	No dose adjustment needed. Do not initiate CAB/RPV IM during or within 2 weeks after tecovirimat treatment. (Refer to Table 24b for interaction with RPV.)
	BIC, CAB (PO), DTG, EVG/c, RAL	↔ INSTI expected	No dose adjustment needed.
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	All INSTIs	↔ arformoterol or formoterol expected	No dose adjustment needed.
Indacaterol	BIC, CAB (PO and IM), DTG, RAL	↔ indacaterol expected	No dose adjustment needed.
	EVG/c	↑ indacaterol expected	
Olodaterol	BIC, CAB (PO and IM), DTG, RAL	↔ olodaterol expected	No dose adjustment needed.
	EVG/c	↑ olodaterol expected	
Salmeterol	BIC, CAB (PO and IM), DTG, RAL	↔ salmeterol expected	No dose adjustment needed.

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Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ salmeterol possible	Do not coadminister due to the potential for increased risk of salmeterol-associated cardiovascular events.
Cardiac Medications			
Amiodarone	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ amiodarone expected	No dose adjustment needed.
	EVG/c	↑ INSTI possible ↑ amiodarone possible	Do not coadminister unless the benefits outweigh the risks. If coadministration is necessary, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone concentrations.
Bepridil, Digoxin, Disopyramide, Dronedarone, Flecainide, Systemic Lidocaine, Mexilitine, Propafenone, Quinidine	BIC, CAB (PO and IM), DTG	↔ expected for the listed antiarrhythmics, except for disopyramide ↑ disopyramide possible	No dose adjustment needed. Monitor for disopyramide-related adverse events.
	RAL	↔ expected for the listed antiarrhythmics	No dose adjustment needed.
	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and ↔ AUC	Therapeutic drug monitoring for antiarrhythmics, if available, is recommended.
Beta Blockers (e.g., metoprolol, timolol)	BIC, CAB (PO and IM), DTG, RAL	↔ beta blocker expected	No dose adjustment needed.
	EVG/c	↑ beta blocker possible	Beta blocker dose may need to be decreased; adjust dose based on clinical response. Consider using an alternative ARV or a beta blocker that is not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
Bosentan	BIC, DTG	↓ BIC and DTG possible	No dose adjustment needed.
	CAB (PO and IM)	↔ bosentan expected	Consider using alternative ARV or an alternative to bosentan because bosentan may ↓ RPV, which is co-packaged and coadministered with CAB IM. If bosentan is used with RPV, monitor virologic response to ART.
	RAL	↔ bosentan expected	No dose adjustment needed.
	EVG/c	↑ bosentan possible	In Patients on EVG/c **≥10 Days** • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In Patients on Bosentan Who Require EVG/c • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Calcium Channel Blockers	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment needed.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ CCB expected	No dose adjustment needed.
	EVG/c	↑ CCB possible	Titrate CCB dose and monitor for CCB efficacy and adverse events.
Dofetilide	BIC, DTG	↑ dofetilide expected	Contraindicated.
	CAB (PO and IM), RAL	↔ dofetilide expected	No dose adjustment needed.
	EVG/c	↑ dofetilide possible	Do not coadminister.
Eplerenone	BIC, CAB (PO and IM), DTG, RAL	↔ eplerenone expected	No dose adjustment needed.
	EVG/c	↑ eplerenone expected	Contraindicated.
Ivabradine	BIC, CAB (PO and IM), DTG, RAL	↔ ivabradine expected	No dose adjustment needed.
	EVG/c	↑ ivabradine expected	Contraindicated.
Ranolazine	BIC, CAB (PO and IM), DTG, RAL	↔ ranolazine expected	No dose adjustment needed.
	EVG/c	↑ ranolazine expected	Contraindicated.
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ glucocorticoid expected	No dose adjustment needed.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, CAB (PO and IM), DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid possible	Do not coadminister unless the potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider using an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid possible ↓ EVG possible	Do not coadminister unless the potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects. Coadministration can result in adrenal insufficiency and Cushing's syndrome.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Dexamethasone Systemic	BIC	↓ BIC possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	CAB (PO and IM), DTG, RAL	↔ INSTI expected	No dose adjustment needed.
	EVG/c	↓ EVG and COBI possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, CAB (PO and IM), DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministration is necessary, monitor for adrenal insufficiency and Cushing's syndrome.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, CAB (PO and IM), DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid expected	Do not coadminister. Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	BIC, CAB (PO and IM), RAL	↔ daclatasvir expected	No dose adjustment needed.
	DTG	↔ daclatasvir	No dose adjustment needed.
	EVG/c	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
Dasabuvir plus Ombitasvir/Paritaprevir/RTV	BIC	↔ BIC expected	No dose adjustment needed.
	CAB (PO and IM)	↔ CAB expected ↑ RPV IM expected	Do not coadminister due to potential for QTc prolongation with higher concentrations of RPV. RPV is co-packaged and coadministered with CAB IM.
	DTG	↔ DTG, dasabuvir, plus ombitasvir/paritaprevir/RTV	No dose adjustment needed.
	EVG/c	No data	Do not coadminister.
	RAL	RAL AUC ↑ 134%	No dose adjustment needed.
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment needed.
	CAB (PO and IM)	↔ CAB, elbasvir, and grazoprevir expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	DTG	↔ DTG ↔ elbasvir ↔ grazoprevir	No dose adjustment needed.
	EVG/c	↑ elbasvir expected ↑ grazoprevir expected	Do not coadminister.
	RAL	↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir ↔ elbasvir ↔ grazoprevir	No dose adjustment needed.
Glecaprevir/Pibrentasvir	BIC, CAB (PO and IM)	↔ BIC or CAB expected	No dose adjustment needed.
	DTG	↔ DTG and glecaprevir/ pibrentasvir	No dose adjustment needed.
	RAL	No significant effect RAL AUC ↑ 47%	
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
Ledipasvir/Sofosbuvir	BIC, DTG, RAL	↔ BIC, DTG, and RAL	No dose adjustment needed.
	CAB (PO and IM)	↔ CAB expected	No dose adjustment needed.
	EVG/c/TDF/ FTC	↑ TDF expected ↑ ledipasvir expected	Do not coadminister.
	EVG/c/TAF/ FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment needed.
Sofosbuvir	BIC, CAB (PO and IM), DTG, EVG/C	↔ INSTI expected ↔ sofosbuvir expected	No dose adjustment needed.
	RAL	↔ RAL and sofosbuvir	No dose adjustment needed.
Sofosbuvir/Velpatasvir	BIC, DTG, RAL	↔ sofosbuvir and velpatasvir	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events.
	CAB (PO and IM)	↔ CAB expected ↔ sofosbuvir and velpatasvir expected	

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↔ EVG/c/TAF/FTC Velpatasvir AUC ↑ 50%	
Sofosbuvir/ Velpatasvir/ Voxilaprevir	BIC	When Administered With Sofosbuvir/ Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg • ↔ BIC, sofosbuvir, velpatasvir, voxilaprevir	No dose adjustment needed.
	EVG/c	When Administered With Sofosbuvir/ Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
	BIC, CAB (PO and IM), DTG, RAL	↔ INSTI expected ↔ sofosbuvir, velpatasvir, and voxilaprevir expected	No dose adjustment needed.
Herbal Products			
St. John's Wort	BIC, CAB (PO and IM), DTG	↓ BIC and DTG possible	Do not coadminister.
	EVG/c	↓ EVG and COBI expected	Contraindicated.
Hormonal Therapies			
Contraceptives: Non-Oral	BIC, CAB (PO and IM), DTG, RAL	Etonogestrel (subdermal implant) ↑ 27% with DTG ↔ expected with BIC, CAB, RAL	No dose adjustment needed.
	EVG/c	No data	No data available to make dose recommendation.
Contraceptives: Oral	BIC, DTG, RAL	↔ ethinyl estradiol and norgestimate ↔ INSTI	No dose adjustment needed.
	CAB (PO and IM)	↔ ethinyl estradiol and levonorgestrel with CAB PO	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ > 2-fold Ethinyl estradiol AUC ↓ 25% and C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and may include insulin resistance, dyslipidemia, acne, and venous thrombosis. Decreased ethinyl estradiol may lead to more intermenstrual bleeding. Weigh the risks and benefits of using the drug and consider using an alternative ARV or contraceptive method.
		↑ drospirenone possible	Clinical monitoring is recommended due to the potential for hyperkalemia. Consider using alternative ARV or contraceptive method.
Gender-Affirming Therapy	BIC, CAB (PO and IM), DTG, EVG/c, RAL	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed.
	BIC, CAB (PO and IM), DTG, RAL	↔ estrogen expected	No dose adjustment needed.
		↔ testosterone expected	No dose adjustment needed.
	EVG/c	↑ estradiol possible ↑ cyproterone, dutasteride, and finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations.
		↑ testosterone possible	Monitor masculinizing effects of testosterone and monitor for adverse effects. Adjust testosterone dose as necessary.
Menopausal Replacement Therapy	BIC, CAB (PO and IM), DTG, RAL	↔ estrogen expected with estradiol or conjugated estrogen (equine and synthetic) ↔ drospirenone, medroxyprogesterone, and micronized progesterone expected	No dose adjustment needed.
	EVG/c	↓ or ↑ estrogen possible ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, CAB (PO and IM), DTG, RAL	↔ immunosuppressant expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c	↑ immunosuppressant possible	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant. Monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ atorvastatin expected	No dose adjustment needed.
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Titrate statin dose carefully. Administer the lowest effective dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
Lomitapide	BIC, CAB (PO and IM), DTG, RAL	↔ lomitapide expected	No dose adjustment needed.
	EVG/c	↑ lomitapide expected	Contraindicated.
Lovastatin	BIC, CAB (PO and IM), DTG, RAL	↔ lovastatin expected	No dose adjustment needed.
	EVG/c	Significant ↑ lovastatin expected	Contraindicated.
Pitavastatin, Pravastatin	BIC, CAB (PO and IM), DTG, RAL	↔ statin expected	No dose adjustment needed.
	EVG/c	No data	No data available for dose recommendation.
Rosuvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ rosuvastatin expected	No dose adjustment needed.
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest effective dose while monitoring for adverse events.
Simvastatin	BIC, CAB (PO and IM), DTG, RAL	↔ simvastatin expected	No dose adjustment needed.
	EVG/c	Significant ↑ simvastatin expected	Contraindicated.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine	BIC, CAB (PO and IM), DTG	↔ buprenorphine and norbuprenorphine (active metabolite) expected	No dose adjustment needed.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sublingual, buccal, or implant	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 42% and C_{min} ↑ 57%	No dose adjustment needed. Monitor for adverse events of buprenorphine. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ buprenorphine and norbuprenorphine (active metabolite) (sublingual) ↔ buprenorphine or norbuprenorphine (active metabolite) expected (implant)	No dose adjustment needed.
Fentanyl	BIC, CAB (PO and IM), DTG, RAL	↔ fentanyl expected	No dose adjustment needed.
	EVG/c	↑ fentanyl	Monitor for fentanyl efficacy and adverse events, including potentially fatal respiratory depression.
Lofexidine	BIC, CAB (PO and IM), DTG, RAL	↔ lofexidine expected	No dose adjustment needed.
	EVG/c	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	All INSTIs	↔ methadone	No dose adjustment needed.
Tramadol	BIC, CAB (PO and IM), DTG, RAL	↔ tramadol and M1 (active metabolite) expected	No dose adjustment needed.
	EVG/c	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.
PDE5 Inhibitors			
Avanafil	BIC, CAB (PO and IM), DTG, RAL	↔ avanafil expected	No dose adjustment needed.
	EVG/c	No data	Do not coadminister.
Sildenafil	BIC, CAB (PO and IM), DTG, RAL	↔ sildenafil expected	No dose adjustment needed.
	EVG/c	↑ sildenafil expected	For Treatment of Erectile Dysfunction • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. Contraindicated for treatment of PAH.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Tadalafil	BIC, CAB (PO and IM), DTG, RAL	↔ tadalafil expected	No dose adjustment needed.
	EVG/c	↑ tadalafil expected	For Treatment of Erectile Dysfunction • Start with tadalafil 5 mg. Do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH *In Patients on EVG/c >7 Days* • Start with tadalafil 20 mg once daily. Increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require EVG/c* • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, CAB (PO and IM), DTG, RAL	↔ vardenafil expected	No dose adjustment needed.
	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Alprazolam, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	BIC, CAB (PO and IM), DTG, RAL	↔ benzodiazepine expected	No dose adjustment needed.
	EVG/c	↑ benzodiazepine possible	Dose reduction of benzodiazepine may be necessary. Initiate with a low dose and monitor for benzodiazepine-related adverse events. Consider using an alternative benzodiazepine, such as lorazepam, oxazepam, or temazepam.
Midazolam, Triazolam	BIC, CAB (PO and IM), RAL	↔ benzodiazepine expected	No dose adjustment needed.
	DTG	With DTG 25 mg • ↔ midazolam AUC	No dose adjustment needed.
	EVG/c	↑ midazolam expected ↑ triazolam expected	Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c. Parenteral midazolam can be administered in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Suvorexant	BIC, CAB (PO and IM), DTG, RAL	↔ suvorexant expected	No dose adjustment needed.
	EVG/c	↑ suvorexant expected	Do not coadminister.
Zolpidem	BIC, CAB (PO and IM), DTG, RAL	↔ zolpidem expected	No dose adjustment needed.
	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction of zolpidem may be necessary.
Miscellaneous Drugs			
Calcifediol	BIC, CAB (PO and IM), DTG, RAL	↔ calcifediol expected	No dose adjustment needed.
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required. Monitor serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations.
Cisapride	BIC, CAB (PO and IM), DTG, RAL	↔ cisapride expected	No dose adjustment needed.
	EVG/c	↑ cisapride expected	Contraindicated.
Colchicine	BIC, CAB (PO and IM), DTG, RAL	↔ colchicine expected	No dose adjustment needed.
	EVG/c	↑ colchicine expected	Do not coadminister in patients with hepatic or renal impairment. For Treatment of Gout Flares • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. For Treatment of Familial Mediterranean Fever • Do not exceed colchicine 0.6 mg once daily or 0.3 mg twice daily.
Dronabinol	BIC, CAB (PO and IM), DTG, RAL	↔ dronabinol expected	No dose adjustment needed.
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse events.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Eluxadoline	BIC, CAB (PO and IM), DTG, RAL	↔ eluxadoline expected	No dose adjustment needed.
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse events.
Ergot Derivatives	BIC, CAB (PO and IM), DTG, RAL	↔ dihydroergotamine, ergotamine, and methylergonovine expected	No dose adjustment needed.
	EVG/c	↑ dihydroergotamine, ergotamine, and methylergonovine expected	Contraindicated.
Flibanserin	BIC, CAB (PO and IM), DTG, RAL	↔ flibanserin expected	No dose adjustment needed.
	EVG/c	↑ flibanserin expected	Contraindicated.
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals Note: Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids.	BIC	↔ BIC AUC if administered simultaneously with Fe or Ca and food BIC AUC ↓ 33% if administered simultaneously with $CaCO_3$ under fasting conditions BIC AUC ↓ 63% if administered simultaneously with Fe under fasting conditions	With Supplements That Contain Ca or Fe • Administer BIC and supplements that contain Ca or Fe together with food. Do not coadminister BIC under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.
	CAB	↓ INSTI possible	If coadministration is necessary, administer INSTI at least 2 hours before or at least 4 hours after supplements that contain polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic response. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
	DTG	DTG AUC ↓ 39% if administered simultaneously with $CaCO_3$ under fasting conditions DTG AUC ↓ 54% if administered simultaneously with Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	With Supplements That Contain Ca or Fe • Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hours before or at least 6 hours after supplement. Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.

Table 24d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	EVG/c, RAL	↓ INSTI possible	If coadministration is necessary, administer INSTI at least 2 hours before or at least 6 hours after supplements that contain polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic response. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: Al = aluminum; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; AUC = area under the curve; BIC = bictegravir; Ca = calcium; CAB = cabotegravir; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; ECG = electrocardiogram; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; GI = gastrointestinal; IM = intramuscular; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PO = orally; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; Zn = zinc

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Updated: September 01, 2022
Reviewed: September 01, 2022

In the table below, "no dose adjustment needed" indicates that the U.S. Food and Drug Administration–approved dose of maraviroc (MVC) 300 mg twice daily should be used. Recommendations for managing a particular drug interaction may differ, depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Concomitant Drug Class/Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials - Macrolides		
Azithromycin	↔ MVC expected	No dose adjustment needed.
Clarithromycin	↑ MVC possible	MVC 150 mg twice daily
Erythromycin	↑ MVC possible	No dose adjustment needed.
Anticonvulsants		
Carbamazepine, Phenobarbital, Phenytoin	↓ MVC possible	If Used Without a Strong CYP3A Inhibitor • MVC 600 mg twice daily If Used With a Strong CYP3A Inhibitor • MVC 150 mg twice daily
Eslicarbazepine	↓ MVC possible	Consider alternative ARV or anticonvulsant.
Oxcarbazepine	↓ MVC possible	Consider alternative ARV or anticonvulsant.
Antifungals		
Fluconazole	↑ MVC possible	No dose adjustment needed.
Isavuconazole	↑ MVC possible	No dose adjustment needed.
Itraconazole	↑ MVC possible	MVC 150 mg twice daily
Posaconazole	↑ MVC possible	MVC 150 mg twice daily
Voriconazole	↑ MVC possible	MVC 150 mg twice daily

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Antimycobacterials		
Rifabutin	MVC AUC ↔ and C_{min} ↓ 30%	If Used *Without* a Strong CYP3A Inhibitor • MVC 300 mg twice daily If Used *With* a Strong CYP3A Inhibitor • MVC 150 mg twice daily
Rifampin	MVC AUC ↓ 63%	If Used *Without* a Strong CYP3A Inhibitor • MVC 600 mg twice daily If Used *With* a Strong CYP3A Inhibitor • Consider alternative ARV or antimycobacterial.
Rifapentine	↓ MVC expected	Do not coadminister.
Antivirals - Orthopoxviruses (Smallpox, Mpox)		
Brincidofovir	↔ MVC expected	No dose adjustment needed.
Cidofovir	↔ MVC expected	No dose adjustment needed.
Tecovirimat	When Given With MVC Without a Boosted PI or Other Potent CYP3A4 Inhibitors • ↓ MVC possible but not expected to be clinically relevant When Given With MVC Plus a Boosted PI or Other Potent CYP3A4 Inhibitors • ↑ MVC expected	If Used *Without* a Strong CYP3A Inhibitor • No dose adjustment needed. If Used *With* a Strong CYP3A Inhibitor • MVC 150 mg twice daily
Hepatitis C Direct-Acting Antivirals		
Daclatasvir	↔ MVC expected ↔ daclatasvir expected	No dose adjustment needed.
Dasabuvir plus Ombitasvir/Paritaprevir/RTV	↑ MVC expected	Do not coadminister.
Elbasvir/Grazoprevir	↔ MVC expected	No dose adjustment needed.
Ledipasvir/Sofosbuvir	↔ MVC expected	No dose adjustment needed.
Glecaprevir/Pibrentasvir	↔ MVC expected	No dose adjustment needed.
Simeprevir	↔ MVC expected	No dose adjustment needed.
Sofosbuvir	↔ MVC expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir	↔ MVC expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir/Voxilaprevir	↔ MVC expected	No dose adjustment needed.

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

Herbal Products		
St. John's Wort	↓ MVC expected	Do not coadminister.
Hormonal Therapies		
Hormonal Contraceptives	↔ ethinyl estradiol or levonorgestrel	No dose adjustment needed.
Menopausal Hormone Replacement Therapy	↔ MVC or hormone replacement therapies expected	No dose adjustment needed.
Gender-Affirming Hormone Therapies	↔ MVC or gender-affirming hormones expected	No dose adjustment needed.
Antiretroviral Drugs		
Attachment Inhibitor		
FTR[a]	MVC AUC ↑ 25% ↔ TMR[a]	No dose adjustment needed.
INSTIs		
BIC, CAB PO and IM, DTG	↔ MVC expected	No dose adjustment needed.
EVG/c	↑ MVC possible	MVC 150 mg twice daily
RAL	MVC AUC ↓ 21% RAL AUC ↓ 37%	No dose adjustment needed.
NNRTIs		
DOR, RPV PO and IM	↔ MVC expected	No dose adjustment needed.
EFV	MVC AUC ↓ 45%	If Used *Without* a Strong CYP3A Inhibitor • MVC 600 mg twice daily If Used *With* a Strong CYP3A Inhibitor • MVC 150 mg twice daily
ETR	MVC AUC ↓ 53%	If Used *Without* a Strong CYP3A Inhibitor • MVC 600 mg twice daily If Used *With* a Strong CYP3A Inhibitor • MVC 150 mg twice daily
NVP	↔ MVC AUC	If Used *Without* a Strong CYP3A Inhibitor • MVC 300 mg twice daily If Used *With* a Strong CYP3A Inhibitor • MVC 150 mg twice daily

Table 24e. Drug Interactions Between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents)

PIs		
ATV Unboosted, ATV/c, ATV/r	With Unboosted ATV • MVC AUC ↑ 257% With (ATV/r 300 mg/100 mg) Once Daily • MVC AUC ↑ 388%	MVC 150 mg twice daily
DRV/c, DRV/r	With (DRV/r 600 mg/100 mg) Twice Daily • MVC AUC ↑ 305% With (DRV/r 600 mg/100 mg) Twice Daily and ETR • MVC AUC ↑ 210%	MVC 150 mg twice daily
LPV/r	MVC AUC ↑ 295% With LPV/r and EFV • MVC AUC ↑ 153%	MVC 150 mg twice daily

[a] FTR is a prodrug metabolized to its active moiety, temsavir (TMR). Therefore, the effect on gp120-directed attachment inhibitor in the table refers to TMR concentrations.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; CAB = cabotegravir; C_{min} = minimum plasma concentration; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Updated: September 01, 2022
Reviewed: September 01, 2022

Fostemsavir (FTR), an HIV-1 gp120-directed attachment inhibitor, is a prodrug of temsavir (TMR). In this table, the effect on gp120-directed attachment inhibitor refers to TMR concentrations. Recommendations for managing a particular drug interaction may differ depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. Providers should exercise their clinical judgement to select the most appropriate alternative medication to use in cases where an interacting drug needs to be replaced with an alternative.

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers		
H2 Receptor Antagonists	↔ TMR	No dose adjustment needed.
Antibacterials – Antimycobacterials		
Rifabutin	With Rifabutin 300 mg Once Daily and Without RTV • TMR AUC ↓ 30% With Rifabutin 150 mg Once Daily and With RTV 100 mg Once Daily • TMR AUC ↑ 66%	If Used *Without* PI/r • No dosage adjustment needed. If Used *With* PI/r • Recommended dose is rifabutin 150 mg once daily. • No dosage adjustment of FTR.
Rifampin	TMR AUC ↓ 72%	Contraindicated.
Rifapentine	↓ TMR expected	Do not coadminister.
Anticonvulsants		
Carbamazepine, Phenobarbital, Phenytoin	↓ TMR expected	Contraindicated.
Antivirals – Orthopoxviruses (Smallpox, Mpox)		
Brincidofovir	↑ brincidofovir possible	Give FTR dose at least 3 hours after administering brincidofovir, and monitor for brincidofovir-related adverse events (i.e., elevations in ALT/AST and bilirubin and GI adverse events).

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cidofovir	↔ TMR expected	No dose adjustment needed.
Tecovirimat	↔ TMR expected	No dose adjustment needed.
Hepatitis C Direct-Acting Antivirals		
Daclatasvir	↔ expected	No dose adjustment needed.
Dasabuvir plus Ombitasvir/Paritaprevir/RTV	↔ expected	No dose adjustment needed.
Elbasvir/Grazoprevir	↑ grazoprevir expected	Increased grazoprevir exposures may increase the risk of ALT elevations. Use an alternative HCV regimen.
Ledipasvir/Sofosbuvir	↔ expected	No dose adjustment needed.
Glecaprevir/Pibrentasvir	↔ expected	No dose adjustment needed.
Sofosbuvir	↔ expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir	↔ expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir/Voxilaprevir	↑ voxilaprevir expected	Use an alternative HCV regimen if possible.
Herbal Products		
St. John's Wort	↓ TMR expected	Contraindicated.
Hormonal Therapies		
Contraceptives: Oral	ethinyl estradiol AUC ↑ 40% ↔ norethindrone	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[a] or use alternative ARV or contraceptive methods.
Gender-Affirming Hormone Therapies	No data	No data available to make dose recommendation.
Menopausal Hormone Replacement Therapy	No data	No data available to make dose recommendation.
Lipid-Modifying Agents		
Atorvastatin, Fluvastatin, Pitavastatin, Simvastatin	↑ statin possible ↔ expected	Increased statin concentration may not be clinically relevant. Follow clinical guidelines. Administer the lowest effective statin dose while monitoring for adverse events.

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rosuvastatin	Rosuvastatin AUC ↑ 69%	Increased rosuvastatin concentration may not be clinically relevant. Follow clinical guidelines. Administer the lowest effective dose while monitoring for adverse events.
Narcotics and Treatment for Opioid Dependence		
Buprenorphine/naloxone	Buprenorphine AUC ↑ 30% Norbuprenorphine (active metabolite) AUC ↑ 39%	No dose adjustment needed.
Methadone	↔ Total methadone ↔ R(−) methadone (active metabolite) ↔ S(+) methadone	No dose adjustment needed.
Antiretroviral Drugs		
CCR5 Antagonist		
MVC	↔ TMR MVC AUC ↑ 25%	No dose adjustment needed.
INSTIs		
BIC, CAB (IM or PO), DTG, EVG/c	↔ TMR expected	No dose adjustment needed.
RAL plus TDF	↔ TMR	No dose adjustment needed.
NRTIs		
TDF	↔ TMR ↔ TDF	No dose adjustment needed.
NNRTIs		
DOR, RPV (IM or PO)	↔ TMR expected	No dose adjustment needed.
EFV	↓ TMR possible ↔ EFV expected	No dose adjustment needed.
ETR	TMR AUC ↓ 50% ↔ ETR	No dose adjustment needed.

Table 24f. Drug Interactions Between HIV-1 gp120-Directed Attachment Inhibitors and Other Drugs (Including Antiretroviral Agents)

Concomitant Drug Class/ Name	Effect on gp120-Directed Attachment Inhibitor and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
ETR plus DRV/r	TMR C_{max} and AUC ↑ 34% to 53% ↔ DRV, RTV ETR AUC ↑ 28%	No dose adjustment needed.
PIs		
ATV Unboosted, ATV/c	↑ TMR possible ↔ ATV expected	No dose adjustment needed.
ATV/r	TMR C_{max} and AUC ↑ 54% to 58% ↔ ATV, RTV	No dose adjustment needed.
DRV/c	TMR C_{max} and AUC ↑ 79% to 97% ↔ DRV, RTV expected	No dose adjustment needed.
DRV/r	TMR C_{max} and AUC ↑ 52% to 63% ↔ DRV, RTV	No dose adjustment needed.
LPV/r	↑ TMR possible ↔ LPV expected	No dose adjustment needed.

[a] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations also may be available.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Key: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; C_{max} = maximum plasma concentration; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; GI = gastrointestinal; INSTI = integrase strand transfer inhibitor; HCV = hepatitis C virus; IM = intramuscular; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted PI; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TMR = temsavir.

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

Updated: June 3, 2021
Reviewed: June 3, 2021

Note: Interactions associated with DLV, FPV, IDV, NFV, TPV, and SQV are **not** included in this table. Please refer to the Food and Drug Administration product labels for information regarding interactions between these drugs and other concomitant drugs.

Rilpivirine (RPV) intramuscular (IM) is not included in this table, because the combination of cabotegravir IM plus RPV IM is a two-drug co-packaged product. Therefore, RPV IM is not expected to be used as a protease inhibitor.

PIs		NNRTIs				
		DOR	EFV	ETR	NVP	RPV
ATV Unboosted	PK Data	↑ DOR expected ↔ ATV expected	↔ EFV ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ↔ ATV AUC and C_{min} ↓ 47%	↑ NVP possible ↓ ATV possible	↑ RPV PO possible ↔ ATV expected
	Dose	No dose adjustment needed.	Do not coadminister.	Do not coadminister.	Do not coadminister.	No dose adjustment needed.
ATV/c	PK Data	↑ DOR expected ↔ ATV expected	↔ EFV expected ↓ ATV possible ↓ COBI possible	↑ ETR possible ↓ ATV possible ↓ COBI possible	↑ NVP possible ↓ ATV possible ↓ COBI possible	↑ RPV PO possible ↔ ATV expected
	Dose	No dose adjustment needed.	ATV/c in ART-Naive Patients • ATV 400 mg plus COBI 150 mg once daily • Do not use coformulated ATV 300 mg/ COBI 150 mg.	Do not coadminister.	Do not coadminister.	No dose adjustment needed.

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

			ATV/c in ART-Experienced Patients • Do not coadminister. No dose adjustment needed for EFV.			
ATV/r	PK Data	↑ DOR expected ↔ ATV expected	↔ EFV expected (ATV 400 mg plus RTV 100 mg) Once Daily • ATV concentrations similar to (ATV 300 mg plus RTV 100 mg) without EFV	(ATV 300 mg plus RTV 100 mg) Once Daily • ETR AUC and C_{min} both ↑ ~30% • ↔ ATV AUC and C_{min}	(ATV 300 mg plus RTV 100 mg) Once Daily • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV PO possible ↔ ATV expected
	Dose	No dose adjustment needed.	ATV/r in ART-Naive Patients • (ATV 400 mg plus RTV 100 mg) once daily ATV/r in ART-Experienced Patients: • Do not coadminister. No dose adjustment needed for EFV.	No dose adjustment needed.	Do not coadminister.	No dose adjustment needed.
DRV/c	PK Data	↑ DOR expected ↔ DRV expected	↔ EFV expected ↓ DRV possible ↓ COBI possible	ETR 400 mg Once Daily with (DRV 800 mg plus COBI 150 mg) Once Daily • ↔ ETR AUC and C_{min} • ↔ DRV AUC and C_{min} ↓ 56% • COBI AUC ↓ 30% and C_{min} ↓ 66%	↑ NVP possible ↓ DRV possible ↓ COBI possible	↔ DRV expected ↑ RPV PO possible

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

	Dose	No dose adjustment needed.	Do not coadminister.	Do not coadminister.	Do not coadminister.	No dose adjustment needed.
DRV/r	PK Data	↑ DOR expected ↔ DRV expected	With (DRV 300 mg plus RTV 100 mg) Twice Daily • EFV AUC ↑ 21% • ↔ DRV AUC and C_{min} ↓ 31%	ETR 100 mg Twice Daily with (DRV 600 mg plus RTV 100 mg) Twice Daily • ETR AUC ↓ 37% and C_{min} ↓ 49% • ↔ DRV	With (DRV 400 mg plus RTV 100 mg) Twice Daily • NVP AUC ↑ 27% and C_{min} ↑ 47% • DRV AUC ↑ 24%[a]	RPV 150 mg PO Once Daily with (DRV 800 mg plus RTV 100 mg) Once Daily • RPV PO AUC ↑ 130% and C_{min} ↑ 178% • ↔ DRV
	Dose	No dose adjustment needed.	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	No dose adjustment needed. Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	No dose adjustment needed.	No dose adjustment needed.
LPV/r	PK Data	↑ DOR expected ↔ LPV expected	↔ EFV expected With LPV/r 500 mg/125 mg[b] Twice Daily • LPV concentration similar to that of LPV/r 400 mg/100 mg twice daily without EFV	ETR AUC ↓ 35% (comparable to the decrease seen with DRV/r) ↔ LPV AUC	↑ NVP possible LPV AUC ↓ 27% and C_{min} ↓ 51%	RPV 150 mg PO Once Daily with LPV/r • RPV PO AUC ↑ 52% and C_{min} ↑ 74% • ↔ LPV
	Dose	No dose adjustment needed.	LPV/r 500 mg/ 125 mg[a] twice daily LPV/r 533 mg/ 133 mg twice daily when using oral solution No dose adjustment needed for EFV.	No dose adjustment needed.	LPV/r 500 mg/ 125 mg[a] twice daily LPV/r 533 mg/133 mg twice daily when using oral solution No dose adjustment needed for NVP.	No dose adjustment needed.

[a] Use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

Key to Symbols

Table 25a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

↑ = increase
↓ = decrease
↔ = no change

Key: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI = cobicistat; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; IDV = indinavir; IM = intramuscular; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = oral; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; TPV = tipranavir

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

Updated: June 3, 2021
Reviewed: June 3, 2021

Recommendations for managing a particular drug interaction may differ depending on whether a new antiretroviral (ARV) drug is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

Information on drug interactions with oral (PO) cabotegravir (CAB) is not included in this table. The CAB PO tablet is not available in retail pharmacies and will be provided directly to patients for short-term use only (PO lead-in and to bridge intramuscular [IM] administration is delayed).

CAB IM and rilpivirine (RPV) IM also are not included in this table because the combination is a two-drug co-packaged product. Therefore, it is not anticipated that they will be used with oral NNRTIs or PIs.

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs					
DOR	PK Data	↔ DOR and BIC expected	↔ DOR DTG AUC ↑ 36% and C_{min} ↑ 27%	↑ DOR expected ↔ EVG	↔ DOR and RAL expected
	Dose	No dose adjustment needed.	No dose adjustment needed.	No dose adjustment needed.	No dose adjustment needed.
EFV	PK Data	↓ BIC expected	With DTG 50 mg Once Daily • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, and EFV possible	With RAL 400 mg Twice Daily • RAL AUC ↓ 36% and C_{min} ↓ 21% With RAL 1,200 mg Once Daily • ↔ RAL AUC and C_{min}

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
	Dose	Do not coadminister.	In Patients Without INSTI Resistance • DTG 50 mg twice daily In Patients with Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance • Consider alternative combination.	Do not coadminister.	No dose adjustment needed.
ETR	PK Data	↓ BIC expected	ETR 200 mg Twice Daily plus DTG 50 mg Once Daily • DTG AUC ↓ 71% and C_{min} ↓ 88% ETR 200 mg Twice Daily with (DRV 600 mg plus RTV 100 mg) Twice Daily and DTG 50 mg Once Daily • DTG AUC ↓ 25% and C_{min} ↓ 37% ETR 200 mg Twice Daily with (LPV 400 mg plus RTV 100 mg) Twice Daily and DTG 50 mg Once Daily • DTG AUC ↑ 11% and C_{min} ↑ 28%	↑ or ↓ EVG, COBI, and ETR possible	ETR 200 mg Twice Daily plus RAL 400 mg Twice Daily • ETR C_{min} ↑ 17% • RAL C_{min} ↓ 34%

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
	Dose	Do not coadminister.	Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r. In Patients Without INSTI Resistance • DTG 50 mg once daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r) In Patients with Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance • DTG 50 mg twice daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	Do not coadminister.	RAL 400 mg twice daily Coadministration with RAL 1,200 mg once daily is not recommended.
NVP	PK Data	↓ BIC expected	With DTG 50 mg Once Daily • DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, and NVP possible	No data
	Dose	Do not coadminister.	No dose adjustment needed.	Do not coadminister.	No dose adjustment needed.
RPV	PK Data	No data	With DTG 50 mg Once Daily • ↔ DTG AUC and C_{min} ↑ 22% • ↔ RPV PO AUC and C_{min} ↑ 21%	↑ or ↓ EVG, COBI, and RPV PO possible	↔ RPV PO RAL C_{min} ↑ 27%
	Dose	No dose adjustment needed.	No dose adjustment needed.	Do not coadminister.	No dose adjustment needed.

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
PIs					
ATV	PK Data	ATV 400 mg Once Daily plus BIC 75 mg Single Dose • BIC AUC ↑ 315%	(ATV 400 mg plus DTG 30 mg) Once Daily • DTG AUC ↑ 91% and C_{min} ↑ 180%	↑ or ↓ EVG, COBI, and ATV possible	With Unboosted ATV • RAL AUC ↑ 72% With Unboosted ATV and RAL 1,200 mg • RAL AUC ↑ 67%
	Dose	Do not coadminister.	No dose adjustment needed.	Do not coadminister.	No dose adjustment needed.
ATV/c	PK Data	BIC AUC ↑ 306%	No data	Not applicable	No data
	Dose	Do not coadminister.	No dose adjustment needed.	Do not coadminister two COBI-containing products.	No dose adjustment needed.
ATV/r	PK Data	↑ BIC expected	(ATV 300 mg plus RTV 100 mg) Once Daily plus DTG 30 mg Once Daily • DTG AUC ↑ 62% and C_{min} ↑ 121%	Not applicable	With (ATV 300 mg plus RTV 100 mg) Once Daily • RAL AUC ↑ 41%
	Dose	Do not coadminister.	No dose adjustment needed.	Do not coadminister RTV and COBI.	No dose adjustment needed.
DRV	PK Data	Not applicable	Not applicable	↔ DRV or EVG expected	Not applicable
	Dose	Do not administer DRV without RTV or COBI.	Do not administer DRV without RTV or COBI.	No dose adjustment needed.	Do not administer DRV without RTV or COBI.

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
DRV/c	PK Data	BIC AUC ↑ 74%	DRV/c plus DTG Once Daily • ↔ DTG, DRV, and COBI DTG 50 mg Once Daily and DRV/r Once Daily Switched to DRV/c • DTG C_{min} ↑ 100%	Not applicable	No data
	Dose	No dose adjustment needed.	No dose adjustment needed.	Do not coadminister two COBI-containing products.	No dose adjustment needed.
DRV/r	PK Data	No data	(DRV 600 mg plus RTV 100 mg) Twice Daily with DTG 30 mg Once Daily • DTG AUC ↓ 22% and C_{min} ↓ 38%	Not applicable	With (DRV 600 mg plus RTV 100 mg) Twice Daily • RAL AUC ↓ 29% and C_{min} ↑ 38%
	Dose	No dose adjustment needed.	No dose adjustment needed.	Do not coadminister RTV and COBI.	No dose adjustment needed.
LPV/r	PK Data	No data	With (LPV 400 mg plus RTV 100 mg) Twice Daily and DTG 30 mg Once Daily • ↔ DTG	Not applicable	↓ RAL ↔ LPV/r
	Dose	Consider alternative combination.	No dose adjustment needed.	Do not coadminister RTV and COBI.	No dose adjustment needed.

[a] Refer to DTG product label for details.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no change

Table 25b. Interactions Between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; C_{min} = minimum plasma concentration; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir

Appendix A: Key to Acronyms

Updated: September 21, 2022
Reviewed: September 21, 2022

Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
ATV/c	atazanavir/cobicistat
ATV/r	atazanavir/ritonavir
BIC	bictegravir
CAB	cabotegravir
CAB-LA	cabotegravir long-acting
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DRV/c	darunavir/cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
EVG/c	elvitegravir/cobicistat

Abbreviation	Full Name
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitabine
FTR	fostemsavir
IBA	ibalizumab
IDV	indinavir
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
R5	CCR5-utilizing virus
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
TMP-SMX	trimethoprim-sulfamethoxazole
TMR	temsavir
TPV	tipranavir
TPV/r	tipranavir/ritonavir
ZDV	zidovudine

General Terms

Abbreviation	Definition
17-BMP	beclomethasone 17-monopropionate
ACA	Affordable Care Act
ADAP	AIDS drug assistance program
Ag/Ab	antigen/antibody
Al	aluminum
ALT	alanine aminotransferase
AMP	average manufacturer price
ART	antiretroviral therapy
ARTAS	Anti-Retroviral Treatment and Access to Services
ARV	antiretroviral
ASP	average sale price
AST	aspartate aminotransferase
AUC	area under the curve
AUD	alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
AV	atrioventricular
AWP	average wholesale price
AYA	adolescents and young adults
BID	twice daily
BMD	bone mineral density
BUN	blood urea nitrogen
Ca	calcium
$CaCO_3$	calcium carbonate
CBC	complete blood count

Abbreviation	Definition
CCB	calcium channel blockers
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
COC	combined oral contraceptive
CPI-U	consumer price index-urban
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
D/M	dual/mixed
DAA	direct-acting antiviral
DHA	dihydroartemisinin
DILI	drug-induced liver injury
DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetate
DOT	directly observed therapy

Abbreviation	Definition
EBV	Epstein-Barr virus
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
FCP	federal price ceiling
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
Fe	iron
FUL	federal upper limit
GAHT	gender-affirming hormone therapy
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
gp	glycoprotein
GS	Gilead Sciences
H2	histamine H2 receptor, histamine 2
H2RA	H2 receptor antagonist
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HAV	hepatitis A virus
HbA1C	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

Abbreviation	Definition
HCO_3	bicarbonate
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HHS	U.S. Department of Health and Human Services
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
HR	hazard ratio
HRSA	Health Resources and Services Administration
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HSR	hypersensitivity reaction
HTLV-1	human T-lymphotropic virus-1 type I
IAS–USA	International AIDS Society–USA
IC_{50}	inhibitory concentration
IL	interleukin
IM	intramuscular
IN	integrase
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IPT	isoniazid preventive therapy

Abbreviation	Definition
IRIS	immune reconstitution inflammatory syndrome
ISR	injection site reactions
IUD	intrauterine device
IV	intravenous
K	potassium
LA-ART	long-acting ART
LAI	long-acting injectable
LDL	low-density lipoprotein
LGBTQ	lesbian, gay, bisexual, transgender, or queer
LLOD	lower limits of detection
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MAT	medication-assisted treatment
MATE	multidrug and toxin extrusion transporter
MDR	multidrug resistant
MDR-TB	multidrug-resistant tuberculosis
MDMA	methylenedioxymethamphetamine
MDRP	Medicaid Drug Rebate Program
MET	motivational enhancement therapy
Mg	magnesium
MHC	major histocompatibility complex
MI	motivational interviewing
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
MSM	men who have sex with men

Abbreviation	Definition
MTR	multi-tablet regimen
N/A	not applicable
Na	sodium
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NTD	neural tube defect
OARAC	Office of AIDS Research Advisory Council
OAT	opioid agonist therapy
OATP	organic anion-transporting polypeptide
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
OI	opportunistic infection
ONDCP	Office of National Drug Control Policy
OR	odds ratio
OTP	opioid treatment program
OUD	opioid use disorder
P	phosphorus
P-gp	p-glycoprotein
PAH	pulmonary arterial hypertension
PBM	pharmacy benefit manager
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
PHQ-2	Patient Health Questionnaire-2

Abbreviation	Definition
PEP	post-exposure prophylaxis
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
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone
QTc	QT corrected for heart rate
REPC	Retention through Enhanced Personal Contact
RNA	ribonucleic acid
RT	reverse transcriptase
RWHAP	Ryan White HIV/AIDS Program
SAMHSA	Substance Abuse and Mental Health Services Administration
SJS	Stevens Johnson Syndrome
SMAC	state maximum allowable cost
SMR	sexual maturity rating
SPT	skin patch test
SQ	subcutaneous
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
STR	single-tablet regimen
SUD	substance use disorder
TasP	treatment as prevention

Abbreviation	Definition
TB	tuberculosis
TCA	tricyclic antidepressant
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
THRIVE	Targeting HIV Retention and Improved Viral Load Through Engagement
U = U	Undetectable = Untransmittable
UGT	uridine diphosphate glucuronosyltransferase
UGT1	uridine diphosphate glucuronyl transferase 1 family
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
USPSTF	United States Preventive Services Task Force
USTS	U.S. Transgender Survey
UW	University of Washington
VL	viral load
VPA	valproic acid
WAC	wholesale acquisition cost
WBC	white blood cell
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health
XDR	extensively drug resistant
XR	extended release
Zn	zinc

Study and Trial Names

Acronym	Name
ACTG	AIDS Clinical Trials Group
ADVANCE	Assessing Donor Variability And New Concepts in Eligibility
ARDENT	ACTG A5257 trial
ARTEMIS	Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
ECHO	Evidence for Contraceptive Options in HIV
ENCORE	Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy
FLAIR	First Long-Acting Injectable Regimen
FLAMINGO	Dolutegravir Compared to Darunavir/Ritonavir, Each in Combination With Dual Nucleoside Reverse Transcriptase Inhibitors
HPTN	HIV Prevention Trials Network
NADIA	Nucleosides And Darunavir/Dolutegravir In Africa
NAMSAL	New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries
STaR	Single-Tablet Regimen
START	Strategic Timing of AntiRetroviral Treatment

Appendix B: Drug Characteristics Tables

Appendix B, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Updated: September 21, 2022
Reviewed: September 21, 2022

The following table includes dose recommendations for U.S. Food and Drug Administration–approved coformulated and copackaged antiretroviral regimens. Please see the class-specific drug characteristics tables (Appendix B, Tables 3, 4, 5, and 6) for details about the individual drugs included in these products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. The products in this table are listed by drug class and arranged **in alphabetical order** by trade name within each class.

Trade Name (Abbreviation)	ARV Drugs Included in the Regimen	Dosing Recommendation[a]
INSTI plus Two NRTIs		
Biktarvy (BIC/TAF/FTC)	Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet PO once daily
Genvoya (EVG/c/TAF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet PO once daily with food
Stribild (EVG/c/TDF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily with food
Triumeq Triumeq PD (DTG/ABC/3TC)	Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg Dolutegravir 5-mg/abacavir 60-mg/lamivudine 30-mg tablet for oral suspension	One tablet PO once daily
INSTI plus One NRTI		
Dovato (DTG/3TC)	Dolutegravir 50 mg/lamivudine 300 mg	One tablet PO once daily
PI plus Two NRTIs		
Symtuza (DRV/c/TAF/FTC)	Darunavir 800 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet PO once daily with food
NNRTI plus Two NRTIs		
Atripla (EFV/TDF/FTC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
Complera (RPV/TDF/FTC)	Rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily with food

Appendix B, Table 1. Coformulated and Copackaged Antiretroviral Regimens

Trade Name (Abbreviation)	ARV Drugs Included in the Regimen	Dosing Recommendation[a]
Delstrigo (DOR/TDF/3TC)	Doravirine 100 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily
Odefsey (RPV/TAF/FTC)	Rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet PO once daily with food
Symfi (EFV/TDF/3TC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
Symfi Lo (EFV/TDF/3TC)	Efavirenz 400 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily on an empty stomach, preferably at bedtime
INSTI plus One NNRTI		
Cabenuva (CAB IM and RPV IM)	Cabenuva 600-mg/900-mg kit contains: • CAB 600-mg/3-mL vial and RPV 900-mg/3-mL vial Cabenuva 400-mg/600-mg kit contains: • CAB 400-mg/2-mL vial and RPV 600-mg/2-mL vial	Optional Lead-in with Oral CAB and RPV • CAB 30 mg 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 × 1 dose and RPV 900 mg/3 mL IM × 1 dose • Continuation phase: CAB 400 mg/2 mL IM every 4 weeks and RPV 600 mg/2 mL IM every 4 weeks Every 2-Month IM CAB and RPV • Loading dose: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM once monthly for 2 doses • Continuation phase: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM every 2 months
Juluca (DTG/RPV)	Dolutegravir 50 mg/rilpivirine 25 mg	One tablet PO once daily with food

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 11. When no food restriction is listed, the product can be taken with or without food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; IM = intramuscular; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = orally; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 2. Nucleoside Reverse Transcriptase Inhibitor–Based, Fixed-Dose Combination Tablets for Use as Part of an Antiretroviral Regimen

Updated: Month Day, 2022
Reviewed: Month Day, 2022

The following table includes dose recommendations for U.S. Food and Drug Administration (FDA)–approved dual nucleoside reverse transcriptase inhibitor fixed-dose combination (FDC) products. These FDC tablets are not complete regimens and must be administered in combination with other antiretroviral drugs. FDC products that contain zidovudine (ZDV) have been removed from this table. Please refer to the FDA product labels for information regarding ZDV-containing FDCs. Please see the class-specific drug characteristics tables (Appendix B, Tables 3, 4, 5, and 6) for details about the individual drugs contained in these FDC products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. The FDC tablets in this table are listed by trade name.

Trade Name (Abbreviation)	ARV Drugs Included in the FDC Tablet	Dosing Recommendation[a]
TAF or TDF plus an NRTI		
Descovy (TAF/FTC)	Tenofovir alafenamide 25 mg/emtricitabine 200 mg Tenofovir alafenamide 15 mg/emtricitabine 120 mg	One tablet PO once daily
Cimduo (TDF/3TC)	Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet PO once daily
Truvada (TDF/FTC)	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet PO once daily
Other NRTI-Based, FDC Tablets		
Epzicom (ABC/3TC) Note: Generic product is available.	Abacavir 600 mg/lamivudine 300 mg	One tablet PO once daily

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 11. All FDC tablets listed in this table can be taken without regard to food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; FDC = fixed-dose combination; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; PO = orally; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

Updated: Month Day, 2022
Reviewed: Month Day, 2022

The older nucleoside reverse transcriptase inhibitors didanosine (ddI) and stavudine (d4T) have been discontinued in the United States. Zidovudine (ZDV) is no longer used commonly in clinical practice. Therefore, these antiretrovirals have been removed from this table. Please refer to the U.S. Food and Drug Administration product label for ZDV for information regarding this drug.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* Note: Generic tablet formulation is available.	Ziagen • 300-mg tablet • 20-mg/mL oral solution Generic • 300-mg tablet • Also available as FDC with 3TC FDC Tablets That Contain ABC[c] • Epzicom (ABC/3TC) STRs That Contain ABC[d] • Triumeq and Triumeq PD tablet for oral suspension (DTG/ABC/3TC)	Ziagen • ABC 600 mg PO once daily, *or* • ABC 300 mg PO twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain ABC.	Metabolized by alcohol dehydrogenase and glucuronyl transferase 82% of ABC dose is excreted in the urine as metabolites of ABC. Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 11).	1.5 hours/12–26 hours	Patients who test positive for HLA-B*5701 are at the highest risk of experiencing HSRs. HLA screening should be done before initiating ABC. For patients with a history of HSRs, rechallenge is not recommended. Symptoms of HSRs may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (e.g., sore throat, cough, or shortness of breath). Some cohort studies suggest an increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Emtricitabine (FTC) *Emtriva*	Emtriva • 200-mg hard gelatin capsule • 10-mg/mL oral solution FDC Tablets That Contain FTC[c] • Descovy (TAF/FTC) • Truvada (TDF/FTC) STRs That Contain FTC[d] • Atripla (EFV/TDF/FTC) • Biktarvy (BIC/TAF/FTC) • Complera (RPV/TDF/FTC) • Genvoya (EVG/c/TAF/FTC)	Emtriva *Capsule* • FTC 200 mg PO once daily *Oral Solution* • FTC 240 mg (24 mL) PO once daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain FTC.	86% of FTC dose is excreted renally. See Appendix B, Table 11 for dosing recommendations in patients with renal insufficiency.	10 hours/ >20 hours	Minimal toxicity Hyperpigmentation/skin discoloration Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue FTC.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

	• Odefsey (RPV/TAF/FTC) • Stribild (EVG/c/TDF/FTC) • Symtuza (DRV/c/TAF/FTC)				
Lamivudine (3TC) *Epivir* Note: Generic products are available.	Epivir • 150-mg and 300-mg tablets • 10-mg/mL oral solution Generic • 150-mg and 300-mg tablets • Also available as FDC with ABC FDC Tablets That Contain 3TC[c] • Cimduo (TDF/3TC) • Epzicom (ABC/3TC) STRs That Contain 3TC[d] • Delstrigo (DOR/TDF/3TC) • Dovato (DTG/3TC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC) • Triumeq and Triumeq PD tablet for oral suspension (DTG/ABC/3TC)	Epivir • 3TC 300 mg PO once daily, *or* • 3TC 150 mg PO twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain 3TC.	70% of 3TC dose is excreted renally. See Appendix B, Table 11 for dose recommendations in patients with renal insufficiency.	5–7 hours/18–22 hours	Minimal toxicity Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue 3TC.
Tenofovir Alafenamide (TAF) *Vemlidy* Note: Vemlidy is available as a 25-mg tablet for the treatment of HBV.	FDC Tablets That Contain TAF[c] • Descovy (TAF/FTC) STRs That Contain TAF[d] • Biktarvy (BIC/TAF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Symtuza (DRV/c/TAF/FTC)	See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TAF.	Metabolized by cathepsin A See Appendix B, Table 11 for dosing recommendations in patients 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 patients with HBV/HIV coinfection who discontinue TAF. Diarrhea, nausea, headache Greater weight increase has been reported with TAF than with TDF.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

Tenofovir Disoproxil Fumarate (TDF) *Viread* Note: Generic product is available.	Viread • 150-mg, 200-mg, 250-mg, and 300-mg tablets • 40-mg/g oral powder Generic • 300-mg tablet FDC Tablets that Contain TDF[c] • Cimduo (TDF/3TC) • Truvada (TDF/FTC) STRs that Contain TDF[d] • Atripla (EFV/TDF/FTC) • Complera (RPV/TDF/FTC) • Delstrigo (DOR/TDF/3TC) • Stribild (EVG/c/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	Viread • TDF 300 mg PO once daily, *or* • 7.5 level scoops of oral powder PO once daily (dosing scoop dispensed with each bottle; one level scoop contains 1 g of oral powder). Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). Do not mix oral powder with liquid. See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TDF.	Renal excretion is the primary route of elimination. See Appendix B, Table 11 for dose recommendations in patients 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 patients with HBV/HIV coinfection who discontinue TDF.

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 11. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix B, Table 2 for information about these formulations.

[d] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BMD = bone mineral density; DOR = doravirine; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; EFV = efavirenz; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; PO = orally; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

Updated: Month Day, 2022
Reviewed: Month Day, 2022

The older non-nucleoside reverse transcriptase inhibitor delavirdine (DLV) has been discontinued in the United States and is **not** listed in this table.

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 Also available as part of the STR Delstrigo (DOR/TDF/3TC)[c]	Pifeltro • DOR 100 mg PO once daily See Appendix B, Table 1 for dosing information for Delstrigo.	CYP3A4/5 substrate	15 hours	Nausea Dizziness Abnormal dreams
Efavirenz (EFV) *Sustiva* Note: Generic product is available.	Sustiva • 50-mg and 200-mg capsules • 600-mg tablet Generic • 600-mg tablet STRs that Contain EFV[c] • Atripla (EFV/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	Sustiva • EFV 600 mg PO once daily, at or before bedtime Take on an empty stomach to reduce side effects. See Appendix B, Table 1 for dosing information for STRs that contain EFV.	Metabolized by CYP2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2B6 and 2C19 inducer	40–55 hours	Rash[d] Neuropsychiatric symptoms[e] Serum transaminase elevations Hyperlipidemia QT interval prolongation Use of EFV may lead to false-positive results with some cannabinoid and benzodiazepine screening assays.
Etravirine (ETR) *Intelence*	Intelence • 25-mg, 100-mg, and 200-mg tablets	Intelence • ETR 200 mg PO twice daily Take following a meal.	CYP3A4, 2C9, and 2C19 substrate CYP3A4 inducer CYP2C9 and 2C19 inhibitor	41 hours	Rash, including Stevens-Johnson syndrome[d] HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure), have been reported. Nausea

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Nevirapine (NVP) *Viramune* or *Viramune XR* Note: Generic products are available.	Viramune • 200-mg tablet • 50-mg/5-mL oral suspension Viramune XR • 400-mg tablet Generic • 200-mg tablet • 400-mg extended-release tablet 50-mg/5-mL oral suspension	Viramune • NVP 200 mg PO once daily for 14 days (lead-in period); thereafter, NVP 200 mg PO twice daily, *or* • NVP 400 mg (Viramune XR tablet) PO once daily Take without regard to food. Repeat lead-in period if therapy is discontinued for >7 days. In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in dose until rash resolves, but do not extend lead-in period beyond 28 days.	CYP450 substrate CYP3A4 and 2B6 inducer Contraindicated in patients with moderate to severe hepatic impairment. Dose adjustment is recommended in patients on hemodialysis (see Appendix B, Table 11).	25–30 hours	Rash, including Stevens-Johnson syndrome[d] Symptomatic Hepatitis • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported. • Rash has been reported in approximately 50% of cases. • Symptomatic hepatitis occurs at a significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naive male patients with pre-NVP CD4 counts >400 cells/mm^3. • NVP should not be initiated in these patients unless the benefit clearly outweighs the risk.
Rilpivirine (RPV) *Edurant*	Edurant • 25-mg tablet Coformulated STRs that Contain RPV[c] • Complera (RPV/TDF/FTC) • Juluca (DTG/RPV) • Odefsey (RPV/TAF/FTC) Copackaged Intramuscular Regimen • Cabenuva (CAB plus RPV)	Edurant • RPV 25 mg PO once daily Take with food. See Appendix B, Table 1 for dosing information for coformulated and copackaged regimens that contain RPV.	CYP3A4 substrate	PO: 50 hours IM: 13-28 weeks	Rash[d] Depression, insomnia, headache Hepatotoxicity QT interval prolongation IM Formulation Only • Injection-site reactions (pain, induration, swelling, nodules) • Rare post-injection 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 patients with renal or hepatic insufficiency, see Appendix B, Table 11. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

[c] See Appendix B, Table 1 for information about these formulations.

[d] Rare cases of Stevens-Johnson syndrome have been reported with the use of most NNRTIs; the highest incidence of rash was seen among patients who were receiving NVP.

[e] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (e.g., suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients 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 patients. Late-onset neurotoxicities, including ataxia and encephalopathy, have been reported.

Key: 3TC = lamivudine; ARV = antiretroviral; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; FTC = emtricitabine; HSR = hypersensitivity reaction; IM = intramuscular; IV = intravenous; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PO = orally; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

Appendix B, Table 5. Characteristics of Protease Inhibitors

Updated: Month Day, 2022
Reviewed: Month Day, 2022

The older protease inhibitors indinavir (IDV) and saquinavir (SQV) have been discontinued in the United States; fosamprenavir (FPV), 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 ARV Archived Guidelines section of Clinical Info) or to the U.S. Food and Drug Administration product labels for information regarding these drugs.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Atazanavir (ATV) *Reyataz* (ATV/c) *Evotaz* Note: Generic products of ATV are available.	Reyataz • 150-mg, 200-mg, and 300-mg capsules • 50-mg oral powder/packet Generic • 100-mg, 150-mg, 200-mg, and 300-mg capsules Evotaz • ATV 300-mg/COBI 150-mg tablet	Reyataz *In ARV-Naive Patients* • (ATV 300 mg plus RTV 100 mg) PO once daily; *or* • ATV 400 mg PO once daily • Take with food. *With TDF or in ARV-Experienced Patients* • (ATV 300 mg plus RTV 100 mg) PO once daily • Unboosted ATV is not recommended. • Take with food. *With EFV in ARV-Naive Patients* • (ATV 400 mg plus RTV 100 mg) PO once daily • Take with food. Evotaz • One tablet PO once daily • Take with food. • The use of ATV/c is not recommended for patients who are taking TDF and who have baseline CrCl <70 mL/min (see Appendix B, Table 11 for the equation for calculating CrCl). For dosing recommendations for patients who also are receiving H2 antagonists and PPIs, refer to Table 24a.	ATV • CYP3A4 inhibitor and substrate • Weak CYP2C8 inhibitor • UGT1A1 inhibitor COBI • CYP3A inhibitor and substrate • CYP2D6 inhibitor Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 11).	7 hours	Indirect hyperbilirubinemia Cholelithiasis Nephrolithiasis Renal insufficiency Serum transaminase elevations Hyperlipidemia (especially with RTV boosting) Skin rash Hyperglycemia Fat maldistribution 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 patients who have underlying conduction defects or who are on concomitant medications that can cause PR prolongation.

Appendix B, Table 5. Characteristics of Protease Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Darunavir (DRV) *Prezista* (DRV/c) *Prezcobix*	Prezista • 75-mg, 150-mg, 600-mg, and 800-mg tablets • 100-mg/mL oral suspension Prezcobix • DRV 800-mg/COBI 150-mg tablet Also available as part of the STR Symtuza (DRV/c/TAF/FTC)	Prezista *In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations* • (DRV 800 mg plus RTV 100 mg) PO once daily • Take with food. *In ARV-Experienced Patients with One or More DRV Resistance Mutations* • (DRV 600 mg plus RTV 100 mg) PO twice daily • Take with food. Unboosted DRV is not recommended. Prezcobix • One tablet PO once daily • Take with food. • Not recommended for patients with one or more DRV resistance-associated mutations. • Coadministering Prezcobix and TDF is not recommended for patients with baseline CrCl <70 mL/min (see Appendix B, Table 11 for the equation for calculating CrCl). See Appendix B, Table 1 for dosing information for Symtuza.	DRV • CYP3A4 inhibitor and substrate • CYP2C9 inducer COBI • CYP3A inhibitor and substrate • CYP2D6 inhibitor	15 hours when combined with RTV 7 hours when combined with COBI	Hepatotoxicity Diarrhea, nausea Headache Hyperlipidemia Serum transaminase elevation Hyperglycemia Fat maldistribution An increase in serum creatinine may occur when DRV is administered with COBI. Skin rash: DRV has a sulfonamide moiety; however, incidence and severity of rash are similar in those with or without a sulfonamide allergy—Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported.

Appendix B, Table 5. Characteristics of Protease Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Lopinavir/Ritonavir (LPV/r) *Kaletra* Note: LPV is only available as a component of an FDC tablet that also contains RTV.	Kaletra • LPV/r 200-mg/ 50-mg tablets • LPV/r 100-mg/ 25-mg tablets • LPV/r 400 mg/ 100 mg per 5 mL of oral solution. Oral solution contains 42% alcohol.	Kaletra • LPV/r 400 mg/100 mg PO twice daily, *or* • LPV/r 800 mg/200 mg PO once daily. However, once-daily dosing is not recommended for patients with three or more LPV-associated mutations, pregnant persons, or patients receiving EFV, NVP, carbamazepine, phenytoin, or phenobarbital. *With EFV or NVP in PI-Naive or PI-Experienced Patients* • LPV/r 500-mg/125-mg tablets PO twice daily (use a combination of two LPV/r 200-mg/50-mg tablets plus one LPV/r 100-mg/25-mg tablet to make a total dose of LPV/r 500 mg/125 mg), *or* • LPV/r 533 mg/133 mg oral solution twice daily Food Restrictions *Tablet* • Take without regard to food. *Oral Solution* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	GI intolerance, nausea, vomiting, diarrhea Pancreatitis Asthenia Hyperlipidemia (especially hypertriglyceridemia) Serum transaminase elevation Hyperglycemia Insulin resistance/diabetes mellitus Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia PR interval prolongation QT interval prolongation and Torsades de Pointes have been reported; however, causality could not be established.

Appendix B, Table 5. Characteristics of Protease Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Ritonavir (RTV) *Norvir* Note: Generic is available. Although RTV was initially developed as a PI for HIV treatment, RTV is currently used at a lower dose of 100 mg to 200 mg once or twice daily as a PK enhancer to increase the concentrations of other PIs.	Norvir • 100-mg tablet • 100-mg soft gel capsule • 80-mg/mL oral solution. Oral solution contains 43% alcohol. • 100-mg single packet oral powder Also available as part of the FDC tablet Kaletra (LPV/r)	As a PK Booster (or Enhancer) for Other PIs • RTV 100–400 mg PO per day in one or two divided doses (refer to other PIs for specific dosing recommendations). Food Restrictions *Tablet* • Take with food. *Capsule and Oral Solution* • To improve tolerability, take with food if possible.	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 Taste perversion Hyperglycemia Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 11.

[b] Also see Table 20.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FDC = fixed-dose combination; FTC = emtricitabine; GI = gastrointestinal; H2 = histamine H2 receptor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT1 = uridine diphosphate glucuronyl transferase 1 family

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Updated: Month Day, 2022
Reviewed: Month Day, 2022

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Bictegravir (BIC)	BIC is available only as a component of the STR Biktarvy (BIC/TAF/FTC).[c]	Biktarvy • One tablet PO once daily	CYP3A4 substrate UGT1A1-mediated glucuronidation	~17 hours	Diarrhea Nausea Headache Weight gain
Cabotegravir (CAB)	Available as part of the copackaged IM long-acting regimen Cabenuva (CAB IM and RPV IM) • 400-mg/2-mL vial • 600-mg/3-mL vial Also available as an individual product for IM long-acting pre-exposure prophylaxis Apretude (CAB IM) • 600-mg/3-mL vial Also available in oral tablet formulation Vocabria (CAB PO) • 30-mg tablet • Must be obtained from manufacturer for oral lead-in and oral bridging during administration of Cabenuva (CAB IM/RPV IM)	See Appendix B, Table 1 for dosing information for coformulated and copackaged regimens that contain CAB.	UGT1A1 and UGT1A9-mediated glucuronidation	Oral: 41 hours IM: 6–12 weeks	Headache Nausea Abnormal dreams Anxiety Insomnia Depressive disorders Hepatotoxicity IM formulation only: Injection-site reactions (e.g., pain, induration, swelling, nodules)

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Dolutegravir (DTG) *Tivicay*	Tivicay • 10-mg, 25-mg, and 50-mg tablets • 5-mg soluble tablet STRs that Contain DTG[c] • Dovato (DTG/3TC) • Juluca (DTG/RPV) • Triumeq and Triumeq PD tablet for oral suspension (DTG/ABC/3TC)	In ARV-Naive or ARV-Experienced, INSTI-Naive Patients • DTG 50 mg PO once daily In ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Coadministered with EFV, FPV/r, TPV/r, or Rifampin • DTG 50 PO mg twice daily In INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance • DTG 50 mg PO twice daily See Appendix B, Table 1 for dosing information for STRs that contain DTG.	UGT1A1-mediated glucuronidation Minor substrate of CYP3A4	~14 hours	Insomnia Headache Depression and suicidal ideation (rare; usually occurs in patients with preexisting psychiatric conditions) Weight gain Hepatotoxicity Potential for increased risk of NTDs in infants born to individuals who received DTG around the time of conception is lower than previously reported. Refer to Appendix B, Table 6 for more information. HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury), have been reported.
Elvitegravir (EVG)	EVG is only available as a component of an STR tablet that also contains COBI, FTC, and either TDF or TAF. STRs that Contain EVG[c] • Genvoya (EVG/c/TAF/FTC) • Stribild (EVG/c/TDF/FTC)	Genvoya • One tablet PO once daily with food • See Appendix B, Table 11 for recommendations on dosing in persons with renal insufficiency. Stribild • One tablet PO once daily with food • Not recommended for patients with baseline CrCl <70 mL/min (see Appendix B, Table 11 for the CrCl calculation equation).	EVG • CYP3A and UGT1A1/3 substrate COBI • CYP3A inhibitor and substrate • CYP2D6 inhibitor	EVG/c: ~13 hours	Nausea Diarrhea Depression and suicidal ideation (rare; usually occurs in patients with preexisting psychiatric conditions)

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Raltegravir (RAL) *Isentress* *Isentress HD*	Isentress • 400-mg tablet • 25-mg and 10-mg chewable tablets • 100-mg single-use packet for oral suspension Isentress HD • 600-mg tablet	Isentress *In ARV-Naive Patients or ARV-Experienced Patients* • 400 mg PO twice daily *With Rifampin* • 800 mg PO twice daily Isentress HD *In ARV-Naive or ARV-Experienced Patients 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 patients with preexisting psychiatric conditions)

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 11. When no food restriction is listed, the antiretroviral drug can be taken with or without food.

[b] Also see Table 20.

[c] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; IM = intramuscular; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PO = orally; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; UGT1 = uridine diphosphate glucuronyl transferase 1 family

Appendix B, Table 7. Characteristics of the Fusion Inhibitor

Updated: Month Day, 2022
Reviewed: Month Day, 2022

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Adverse Events[a]
Enfuvirtide (T-20) *Fuzeon*	Fuzeon • Injectable; supplied as lyophilized powder. • Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL. • Refer to prescribing information for storage instruction.	Fuzeon • T-20 90 mg/1 mL SQ twice daily	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.	Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients Increased incidence of bacterial pneumonia HSR occurs in <1% of patients. Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.

[a] Also see Table 20.

Key: HSR = hypersensitivity reaction; SQ = subcutaneous; T-20 = enfuvirtide

Appendix B, Table 8. Characteristics of the CCR5 Antagonist

Updated: Month Day, 2022
Reviewed: Month Day, 2022

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	Selzentry • 150-mg and 300-mg tablets	Selzentry • MVC 150 mg PO twice daily when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers), including PIs (except TPV/r) • MVC 300 mg PO twice daily when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • MVC 600 mg PO twice daily when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take MVC without regard to food.	14–18 hours	CYP3A4 substrate	Abdominal pain Cough Dizziness Musculoskeletal symptoms Pyrexia Rash Upper respiratory tract infections Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions Orthostatic hypotension, especially in patients with severe renal insufficiency

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 11.

[b] Also see Table 20.

Key: CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; T-20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 9. Characteristics of the CD4 Post-Attachment Inhibitor

Updated: Month Day, 2022
Reviewed: Month Day, 2022

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events
Ibalizumab (IBA) *Trogarzo*	Trogarzo • Single-dose 2-mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab	Trogarzo • Administer a single loading dose of IBA 2,000-mg IV infusion over 30 minutes, followed by a maintenance dose of IBA 800-mg IV infusion over 15 minutes every 2 weeks. • See prescribing information for additional instructions for preparing, storing, and administering IBA, and for monitoring patients who are receiving IBA.	~64 hours	Not well defined	Diarrhea Dizziness Nausea Rash Hypersensitivity, including anaphylaxis and infusion-related reactions, have been reported.

Key: IBA = ibalizumab; IV = intravenous

Appendix B, Table 10. Characteristics of the gp120 Attachment Inhibitor

Updated: Month Day, 2022
Reviewed: Month Day, 2022

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events
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 4 times the recommended dose. Use with caution in patients with preexisting heart disease, QTc prolongation, or concomitant use of medications that may prolong QTc interval.

Key: CYP = cytochrome P; FTR = fostemsavir; PO = orally; QTc = corrected QT interval

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Updated: Month Day, 2022
Reviewed: Month Day, 2022

The older antiretroviral drugs fosamprenavir (FPV), nelfinavir (NFV), tipranavir (TPV), and zidovudine (ZDV) have been removed from this table. Please refer to the U.S. Food and Drug Administration product labels for these drugs for recommendations on dosing in adults and adolescents with renal or hepatic insufficiency. See the reference section at the end of this table for creatinine clearance calculation formulas and criteria for Child-Pugh classification.

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
Some FDC products are not recommended in persons with different degrees of renal insufficiency. The recommendations for individual FDCs based on CrCl level are outlined below. • *CrCl <70 mL/min:* Initiation of Stribild is not recommended. • *CrCl <50 mL/min:* FDCs not recommended: Atripla, Cimduo, Complera, Delstrigo, Truvada, Symfi, Symfi-Lo • *CrCl <30 mL/min:* FDCs not recommended: Dovato, Epzicom, Triumeq • *CrCl <30 mL/min and not on HD:* FDCs not recommended: Biktarvy, Descovy, Genvoya, Odefsey, and Symtuza. The component drugs in some of the FDC products listed above may be prescribed as individual formulations with dose adjustment based on CrCl level as indicated below in this table.			
NRTIs			
Abacavir (ABC) *Ziagen*	ABC 300 mg PO twice daily *or* ABC 600 mg PO once daily	No dose adjustment necessary.	*Child-Pugh Class A:* ABC 200 mg PO twice daily (use oral solution) *Child-Pugh Class B or C:* Contraindicated

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

<table>
<tr><th>Generic Name
(Abbreviation)
Trade Name</th><th>Usual Dose[a]</th><th>Dosing in Adults and Adolescents with Renal Insufficiency</th><th>Dosing in Persons with Hepatic Impairment</th></tr>
<tr><td>Abacavir/Lamivudine
(ABC/3TC)
Epzicom</td><td>One tablet PO once daily</td><td>Not recommended if CrCl <30 mL/min. Instead, use the individual component drugs and adjust 3TC dose according to CrCl.</td><td>Child-Pugh Class A: Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these patients.

Child-Pugh Class B or C: Contraindicated due to the ABC component</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>FTC 200-mg oral capsule once daily
or
FTC 240-mg (24-mL) oral solution once daily</td><td>Dose by Formulation
<table><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg every 48 hours</td><td>120 mg every 24 hours</td></tr><tr><td>15–29</td><td>200 mg every 72 hours</td><td>80 mg every 24 hours</td></tr><tr><td><15</td><td>200 mg every 96 hours</td><td>60 mg every 24 hours</td></tr><tr><td>On HD[b]</td><td>200 mg every 24 hours</td><td>240 mg every 24 hours</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td>Lamivudine[c]
(3TC)
Epivir</td><td>3TC 300 mg PO once daily
or
3TC 150 mg PO twice daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>15–29</td><td>1 × 150 mg, then 100 mg every 24 hours</td></tr><tr><td>5–14</td><td>1 × 150 mg, then 50 mg every 24 hours</td></tr><tr><td><5 or on HD</td><td>1 × 50 mg, then 25 mg every 24 hours</td></tr></table></td><td>No dose adjustment necessary.</td></tr>
</table>

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency		Dosing in Persons with Hepatic Impairment
Tenofovir Alafenamide (TAF) *Vemlidy*	Vemlidy is available as a 25-mg tablet for the treatment of HBV.	CrCl (mL/min)	Dose	*Child-Pugh Class B or C*: Not recommended
		<15 and not on HD	Not recommended	
		On HD	One tablet PO once daily	
Tenofovir Alafenamide/Emtricitabine (TAF/FTC) *Descovy*	TAF for HIV treatment is only available as a component of FDC tablets (i.e., in Descovy, Genvoya, Odefsey, Biktarvy, and Symtuza). TAF 10 mg PO daily with EVG/c (Genvoya) or DRV/c (Symtuza) TAF 25 mg PO daily in other FDC tablets	CrCl (mL/min)	Dose	*Child-Pugh Class A or B*: No dose adjustment *Child-Pugh Class C*: No dose recommendation
		<30 and not on HD	Not recommended	
		<30 and on HD	One tablet once daily	
Tenofovir Disoproxil Fumarate (TDF) *Viread*	TDF 300 mg PO once daily	CrCl (mL/min)	Dose	No dose adjustment necessary.
		30–49	300 mg every 48 hours	
		10–29	300 mg twice weekly (every 72–96 hours)	
		<10 and not on HD	No recommendation	
		On HD	300 mg every 7 days	
Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) *Truvada*	One tablet PO once daily	CrCl (mL/min)	Dose	No dose recommendation.
		30–49	One tablet every 48 hours	
		<30 or on HD	Not recommended	

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency		Dosing in Persons with Hepatic Impairment
Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) *Cimduo*	One tablet PO once daily	CrCl (mL/min)	Dose	No dose recommendation.
		<50 or on HD	Not recommended	
NNRTIs				
Doravirine (DOR) *Pifeltro*	DOR 100 mg PO once daily	No dose adjustment required in mild, moderate, or severe renal impairment. Has not been studied in individuals with ESRD or on HD.		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine (DOR/TDF/3TC) *Delstrigo*	One tablet PO once daily	Not recommended if CrCl <50 mL/min.		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied
Efavirenz (EFV) *Sustiva*	EFV 600 mg PO once daily on an empty stomach, preferably at bedtime	No dose adjustment necessary.		No dose recommendation; use with caution in patients with hepatic impairment.
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine (EFV/TDF/FTC) *Atripla*	One tablet PO once daily on an empty stomach, preferably at bedtime	Not recommended if CrCl <50 mL/min. Instead, use the individual component ARVs and adjust TDF and FTC doses according to CrCl level.		No dose recommendation; use with caution in patients with hepatic impairment.
Efavirenz 600 mg/Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi*	One tablet PO once daily on an empty stomach, preferably at bedtime	Not recommended if CrCl <50 mL/min or if patient is on HD. Instead, use the individual component ARVs and adjust TDF and 3TC doses according to CrCl level.		Not recommended for patients with moderate or severe hepatic impairment. Use with caution in patients with mild hepatic impairment.
Efavirenz 400 mg/Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi Lo*	One tablet PO once daily on an empty stomach, preferably at bedtime	Not recommended if CrCl <50 mL/min or if patient is on HD. Instead, use the individual component ARVs and adjust TDF and 3TC doses according to CrCl level.		Not recommended for patients with moderate or severe hepatic impairment. Use with caution in patients with mild hepatic impairment.
Etravirine (ETR) *Intelence*	ETR 200 mg PO twice daily	No dose adjustment necessary.		*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
Nevirapine (NVP) *Viramune* or *Viramune XR*	NVP 200 mg PO twice daily *or* NVP 400 mg PO once daily (using Viramune XR formulation)	No dose adjustment for patients with renal impairment. Patients on HD should receive an additional dose of NVP 200 mg following each dialysis treatment.	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B or C:* Contraindicated
Rilpivirine (RPV PO) *Edurant*	RPV 25 mg PO once daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine IM plus Cabotegravir IM (RPV IM and CAB IM) *Cabenuva*	*Monthly Dosing* • Loading dose: RPV 900 mg/3 mL IM × 1 dose and CAB 600 mg/3 mL IM × 1 dose • Continuation phase: RPV 600 mg/2 mL IM every 4 weeks and CAB 400 mg/2 mL IM every 4 weeks *Every 2-month Dosing* • Loading dose: RPV 900 mg/3 mL IM and CAB 600 mg/3 mL IM monthly for 2 doses • Continuation phase: RPV 900 mg/3 mL IM and CAB 600 mg/3 mL IM every 2 months	No dose adjustment necessary for mild or moderate renal impairment. For patients with severe renal impairment or on HD, increase monitoring for adverse events.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation
Rilpivirine/Tenofovir Alafenamide/Emtricitabine (RPV/TAF/FTC) *Odefsey*	One tablet PO once daily	In Patients on Chronic HD • One tablet once daily. On HD days, administer after dialysis. Not recommended in patients with CrCl <30 mL/min who are not receiving chronic HD.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine (RPV/TDF/FTC) *Complera*	One tablet PO once daily	Not recommended if CrCl <50 mL/min. Instead, use the individual component ARVs and adjust TDF and FTC doses according to CrCl level.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine/Dolutegravir (RPV/DTG) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
PIs			
Atazanavir (ATV) *Reyataz*	ATV 400 mg PO once daily *or* (ATV 300 mg plus RTV 100 mg) PO once daily	No dose adjustment for patients with renal dysfunction who do not require HD. In ARV-Naive Patients on HD • (ATV 300 mg plus RTV 100 mg) once daily In ARV-Experienced Patients on HD • ATV and ATV/r are not recommended	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B:* ATV 300 mg once daily (unboosted) for ARV-naive patients only *Child-Pugh Class C:* Not recommended RTV boosting is not recommended in patients with hepatic impairment.
Atazanavir/Cobicistat (ATV/c) *Evotaz*	One tablet PO once daily	If Used with TDF • Not recommended if CrCl <70 mL/min	Not recommended in patients with hepatic impairment.
Darunavir (DRV) *Prezista*	In ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations • (DRV 800 mg plus RTV 100 mg) PO once daily with food In ARV-Experienced Patients with at Least One DRV Resistance Mutation • (DRV 600 mg plus RTV 100 mg) PO twice daily	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Impairment:* No dose adjustment *In Patients with Severe Hepatic Impairment:* Not recommended
Darunavir/Cobicistat (DRV/c) *Prezcobix*	One tablet PO once daily	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

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (DRV/c/TAF/FTC) *Symtuza*	One tablet PO once daily	In Patients on Chronic HD • One tablet once daily. On HD days, administer after dialysis. Not recommended in patients with CrCl <30 mL/min who are not receiving chronic HD.	Not recommended for patients with severe hepatic impairment.
Lopinavir/Ritonavir (LPV/r) *Kaletra*	(LPV/r 400 mg/100 mg) PO twice daily *or* (LPV/r 800 mg/200 mg) PO once daily	Avoid once-daily dosing in patients on HD.	No dose recommendation; use with caution in patients with hepatic impairment.
Ritonavir (RTV) *Norvir*	As a PI-Boosting Agent • RTV 100–400 mg PO per day	No dose adjustment necessary.	Refer to recommendations for the primary (i.e., boosted) PI.
INSTIs			
Bictegravir/Tenofovir Alafenamide/Emtricitabine (BIC/TAF/FTC) *Biktarvy*	One tablet PO once daily	In Patients on Chronic HD • One tablet once daily. On HD days, administer after dialysis. • Patients receiving chronic HD should be virologically suppressed before Biktarvy is initiated. Not recommended in patients with CrCl <30 mL/min who are not receiving chronic HD.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not recommended
Cabotegravir (CAB PO) *Vocabria*	*Treatment (As Optional Oral Lead-In or As Oral Bridging)* • CAB 30 mg PO once daily, given with RPV 25 mg PO, with food before switching to CAB IM and RPV IM *Pre-exposure Prophylaxis (Optional Oral Lead-In)* • CAB 30 mg PO once daily before switching to CAB IM	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
Cabotegravir (CAB IM) *Apretude*	*Pre-exposure Prophylaxis* • Loading dose: CAB 600 mg/3 mL IM monthly for 2 doses • Continuation phase: CAB 600 mg/3 mL IM every 2 months	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation
Cabotegravir IM plus Rilpivirine IM (CAB IM plus RPV IM) *Cabenuva*	*Monthly Dosing* • Loading dose: CAB 600 mg/3 mL IM × 1 dose and RPV 900 mg/3 mL IM × 1 dose • Continuation phase: CAB 400 mg/2 mL IM every 4 weeks and RPV 600 mg/2 mL IM every 4 weeks *Every 2-month Dosing* • Loading dose: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM monthly for 2 doses • Continuation phase: CAB 600 mg/3 mL IM and RPV 900 mg/3 mL IM every 2 months	No dose adjustment necessary for mild or moderate renal impairment. For patients with severe renal impairment or on HD, increase monitoring for adverse events.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No recommendation
Dolutegravir (DTG) *Tivicay*	DTG 50 mg PO once daily *or* DTG 50 mg PO twice daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not recommended
Dolutegravir/Abacavir/Lamivudine (DTG/ABC/3TC) *Triumeq*	One tablet PO once daily	Not recommended if CrCl <30 mL/min. Instead, use the individual component drugs and adjust 3TC dose according to CrCl.	*Child-Pugh Class A:* Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these patients. *Child-Pugh Class B or C:* Contraindicated due to the ABC component

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
Dolutegravir/Lamivudine (DTG/3TC) *Dovato*	One tablet PO once daily	Not recommended if CrCl <30 mL/min. Instead, use the individual component drugs and adjust 3TC dose according to CrCl.	*Child-Pugh Class C:* Not recommended
Dolutegravir/Rilpivirine (DTG/RPV) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	One tablet PO once daily	In Patients on Chronic HD • One tablet once daily. On HD days, administer after dialysis. Not recommended in patients with CrCl <30 mL/min who are not receiving chronic HD.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* Not recommended
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/c/TDF/FTC) *Stribild*	One tablet PO once daily	EVG/c/TDF/FTC should not be initiated in patients with CrCl <70 mL/min. Discontinue EVG/c/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* Not recommended
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL 400 mg PO twice daily (using Isentress formulation) *or* RAL 1,200 mg PO once daily (using Isentress HD formulation only)	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* No recommendation
Fusion Inhibitor			
Enfuvirtide (T-20) *Fuzeon*	T-20 90 mg SQ twice daily	No dose adjustment necessary.	No dose adjustment necessary.

Appendix B, Table 11. Antiretroviral Dosing Recommendations in Adults and Adolescents with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults and Adolescents with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 8 for detailed dosing information.	In Patients with CrCl <30 mL/min or Patients Who Are on HD *Without Potent CYP3A Inhibitors or Inducers* • MVC 300 mg twice daily; if postural hypotension occurs, reduce to MVC 150 mg twice daily *With Potent CYP3A Inducers or Inhibitors* • Not recommended	No dose recommendations. MVC concentrations will likely be increased in patients with hepatic impairment.
CD4 Post-Attachment Inhibitor			
Ibalizumab (IBA) *Trogarzo*	Loading dose: IBA 2,000 mg IV Maintenance dose: IBA 800 mg IV every 2 weeks	No dose adjustment recommended.	No recommendation.
Fostemsavir (FTR) *Rukobia*	FTR 600 mg PO twice daily	No dose adjustment recommended.	No dose adjustment recommended.

[a] Refer to Appendix B, Tables 1–10 for additional dosing information.

[b] The prescribing information for emtricitabine (Emtriva) recommends a dose of 200 mg every 96 hours for patients with CrCl <15 mL/min or on hemodialysis. However, the prescribing information for several FDC products that contain emtricitabine (including Descovy, Biktarvy, Genvoya, and Odefsey) recommends that the standard dose (emtricitabine 200 mg) can be given once daily in these patients (i.e., on the days of hemodialysis, administer standard dose after completion of dialysis). The recommendation in this table incorporates the dosing guidance from the FDC products.

[c] The prescribing information for lamivudine (Epivir) recommends dosage adjustment from 300 mg once daily to 150 mg once daily for patients with CrCl 30–49 mL/min. However, the prescribing information for several FDC products that contain lamivudine (including Epzicom, Dovato, and Triumeq) recommends no dose adjustment for CrCl 30–49 mL/min. The recommendation in this table incorporates the dosing guidance from the FDC products.

Key: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; ETR = etravirine; EV = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; FTR = Fostemsavir; HBV = hepatitis B virus; HD = hemodialysis; IBA = ibalizumab; IM = intramuscular; INSTI = integrase strand transfer inhibitor; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$	Female: $\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$

Child-Pugh Score			
Component	Points Scored		
	1	2	3
Encephalopathy[a]	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total Bilirubin, *or*	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34–50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified Total Bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin Time (Seconds Prolonged), *or*	<4	4–6	>6
International Normalized Ratio (INR)	<1.7	1.7–2.3	>2.3

[a] Encephalopathy Grades

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin is used for patients who have Gilbert's syndrome or who are taking atazanavir.

Child-Pugh Classification	Total Child-Pugh Score[a]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[a] Sum of points for each component of the Child-Pugh Score.