Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Downloaded from https://aidsinfo.nih.gov/guidelines on 3/24/2018

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Developed by the DHHS 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:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

What's New in the Guidelines? (Last updated October 17, 2017; last reviewed October 17, 2017)

People-First Language

- Based on input from the community, the Adult and Adolescent Guidelines have been updated to include People-First Language. People-First Language is a way of reducing stigma and showing respect for individuals who are living with HIV by focusing on the person instead of the disease (e.g., where the Guidelines might have said "HIV-infected person" in the past, this will now be written as "person with HIV"). The use of People-First Language may also assist as a strategy for retention-in-care measures.

Initiation of Antiretroviral Therapy

- A new subsection was added to discuss the data on the efficacy and feasibility of immediate antiretroviral therapy (ART) initiation on the day of HIV diagnosis.

What to Start

- The classifications of ART regimens recommended for initial therapy have been changed from Recommended, Alternative, and Other to:
  - Recommended Initial Regimens for Most People with HIV; and
  - Recommended Initial Regimens in Certain Clinical Situations.

  Specific regimens are listed in Table 6 of the guidelines.
- Integrase strand transfer inhibitor (INSTI)-based regimens are recommended as initial therapy for most people with HIV. Non-nucleoside reverse transcriptase inhibitor (NNRTI)- and protease inhibitor (PI)-based regimens, including darunavir-based regimens, are recommended in certain clinical situations.
- Since the last revision, longer-term safety data have clarified the relative advantages of tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). TAF has less bone and kidney toxicity, and is therefore particularly advantageous in people at risk for those conditions; TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between TAF and TDF.
- Updates have been made throughout the section with new safety and clinical trial data.
- Under the section on Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used, a new subsection has been added to discuss ongoing clinical trials of various treatment strategies.

What Not to Use

- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) emphasizes that monotherapy with any antiretroviral (ARV) drug should not be used due to increased risk of virologic failure and drug resistance.
- The Panel no longer prohibits the use of efavirenz during the first trimester of pregnancy.

Virologic Failure

- A definition of "low-level viremia" was added to the text.
- The section on Managing Patients with Virologic Failure was restructured, and the section on Managing

Virologic Failure in Different Clinical Scenarios was updated.

- The new Table 10 provides guidance on ARV options for patients with virologic failure.
- Clinicians are advised to maintain patients with hepatitis B virus (HBV)/HIV coinfection on ARV drugs that are active against HBV when switching ART regimens upon virologic failure.
- Links to potential investigational agents for patients with insufficient treatment options have been added to the document.

Regimen Switching in the Setting of Virologic Suppression

- The Panel emphasizes that using PI or INSTI monotherapy as maintenance therapy has been associated with high rates of virologic failure and is therefore not recommended.
- The Panel also notes that, traditionally, the Guidelines have recommended starting ART-naive patients on a regimen consisting of at least three active drugs. However, several studies have now noted that persons with HIV who have sustained viral suppression with no drug resistance may be maintained on regimens including only two active drugs. Results from clinical trials using two-drug maintenance therapy are discussed in this section.
- The section also stresses that when considering a regimen switch in a person with HBV/HIV coinfection, it is important to maintain drugs active against HBV infection in the new regimen.
- Clinical trial data involving several ARV combinations that are currently under investigation are discussed in this section.
- Several ARV combinations that are not recommended for use in maintenance therapy are also included in this section.

Hepatitis B Virus/HIV Coinfection and Hepatitis C Virus/HIV Coinfection

- Both sections have been updated to discuss recent reports regarding reactivation of HBV infection in persons with HBV/hepatitis C virus (HCV) coinfection after starting interferon-free HCV therapy.
    - The Panel recommends that individuals with chronic HBV infection should receive treatment for HBV with nucleoside reverse transcriptase inhibitors (NRTIs) that are active against both HIV and HBV before starting HCV therapy.
- For the HCV section, interactions between new HCV direct-acting agents and ARV drugs have been added to Table 12.

Adherence to the Continuum of Care

- The previous Adherence to Antiretroviral Therapy section has been extensively revised to not only include adherence to therapy, but also adherence to the entire HIV care continuum. As such, the title of this section has been changed to Adherence to the Continuum of Care.
- The section stresses the importance of clinicians working collaboratively with a multidisciplinary team to understand barriers to adherence to the continuum, as well as working with patients to overcome those barriers.
- New evidence-based interventions and best practices to improve adherence are summarized.
- Given their high genetic barriers to resistance, dolutegravir and boosted darunavir are mentioned as medications to consider in persons with proven problems with adherence.

Drug Interactions

- The old Table 18 has been removed from this document. Drugs that are contraindicated or not recommended for use are now all included in the individual ARV drug class tables.
- Throughout the tables, a number of drug classes have been added or expanded, including oral anticoagulants, new oral hypoglycemic agents, and hormonal therapy for menopausal management and gender affirmation.

Additional updates have been made to the following sections:

- Laboratory Testing
- Acute and Recent (Early) HIV Infection
- Adverse Effects of Antiretroviral Agents
- Cost Considerations and Antiretroviral Therapy
- Appendix tables

Prevention of Secondary HIV Transmission

- This section has been removed from the guidelines, as most of the information is discussed in the Initiation of Antiretroviral Therapy section

Table of Contents

List of Tables

HHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Members and Consultants (Last updated October 17, 2017; last reviewed October 17, 2017)

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

Panel Co-Chairs

Roy M. Gulick	Weill Cornell Medicine, New York, NY
Martin S. Hirsch	Massachusetts General Hospital & Harvard Medical School, Boston, MA
H. Clifford Lane	National Institutes of Health, Bethesda, MD

Executive Secretary

Alice K. Pau	National Institutes of Health, Bethesda, MD

Scientific Members

Judith Aberg	Icahn School of Medicine at Mount Sinai, New York, NY
Adaora Adimora	University of North Carolina, Chapel Hill, NC
Allison Agwu	Johns Hopkins University, Baltimore, MD
Roger Bedimo	University of Texas Southwestern Medical Center, Dallas, TX
J. Kevin Carmichael	El Rio Community Health Center, Tucson, AZ
Susan Cu-Uvin	Alpert School of Medicine, Brown University, Providence, RI
Rajesh Gandhi	Massachusetts General Hospital & Harvard Medical School, Boston, MA
Stephen J. Gange	Johns Hopkins University, Baltimore, MD
Edward Gardner	Denver Public Health and University of Colorado, Denver, CO
Thomas Giordano	Baylor College of Medicine, Houston, TX
David Glidden	University of California San Francisco, San Francisco, CA
Peter Hunt	University of California San Francisco, CA
Rami Kantor	Alpert School of Medicine, Brown University, Providence, RI
Marla J. Keller	Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY
Michael Kozal	Yale School of Medicine, New Haven, CT
Jeffrey Lennox	Emory University, Atlanta, GA
Susanna Naggie	Duke University, Durham, NC
Richard W. Price	University of California San Francisco, San Francisco, CA
James Raper	University of Alabama at Birmingham, Birmingham, AL
Daniel Reirden	University of Colorado & Children's Hospital of Colorado, Aurora, CO
Kimberly Scarsi	University of Nebraska Medical Center, Omaha, NE
Serena Spudich	Yale School of Medicine, New Haven, CT
Susan Swindells	University of Nebraska Medical Center, Omaha, NE
Pablo Tebas	University of Pennsylvania, Philadelphia, PA
Zelalem Temesgen	Mayo Clinic, Rochester, MN

Melanie Thompson	AIDS Research Consortium of Atlanta, Atlanta, GA
Phyllis Tien	University of California San Francisco, San Francisco, CA
Rochelle Walensky	Massachusetts General Hospital & Harvard Medical School, Boston, MA

Community Members

Danielle Campbell	Los Angeles, CA
David Evans	Project Inform, South Pasadena, CA
Tim Horn	Treatment Action Group, New York NY
Andy Kaytes	AIDS Treatment Activists Coalition, San Diego, CA
Jeff Taylor	AIDS Treatment Activists Coalition, Palm Springs, CA
Steven Vargas	Association for the Advancement of Mexican Americans (AAMA), Houston, TX

Members Representing Department of Health and Human Services Agencies

John T. Brooks	Centers for Disease Control and Prevention, Atlanta, GA
Laura Cheever	Health Resources and Services Administration, Rockville, MD
Rohan Hazra	National Institutes of Health, Bethesda, MD
Henry Masur	National Institutes of Health, Bethesda, MD
Adam Sherwat	Food and Drug Administration, Silver Spring, MD
Kimberly Struble	Food and Drug Administration, Silver Spring, MD

Non-Voting Observers

Safia Kuriakose	Leidos Biomedical Research, Inc., in support of National Institute of Allergy and Infectious Diseases, National Institutes of Health, Frederick, MD
George Siberry	National Institutes of Health, Bethesda, MD

Pharmacology Consultants

Sarita Boyd	Food and Drug Administration, Silver Spring, MD
Lauren Cirrincione	University of Nebraska Medical Center, Omaha, NE
Safia Kuriakose	Leidos Biomedical Research, Inc., in support of National Institute of Allergy and Infectious Diseases, National Institutes of Health, Frederick, MD

The Panel would also like to acknowledge the assistance of Nicole Winchester of the National Institutes of Health for her assistance in the Drug-Drug Interaction section of the guidelines.

Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2016 to February 2017) (page 1 of 3)

Panel Member	Status	Company	Relationship
Judith Aberg	M	• Bristol-Myers Squibb • Gilead • Merck	• Research support • Research support • Advisory board
Adaora Adimora	M	• Gilead	• Research support
Allison Agwu	M	• Gilead	• Advisory board
Roger Bedimo	M	• Bristol-Myers Squibb • Merck • Theratechnologies	• Advisory board; Research support • Advisory board; Research support • Advisory board
John T. Brooks	M	None	N/A
Danielle Campbell	M	None	N/A
Kevin Carmichael	M	None	N/A
Laura W. Cheever	M	None	N/A
Susan Cu-Uvin	M	None	N/A
David Evans	M	• Bristol-Myers Squibb • ViiV • Merck • Gilead	• Advisory board • Advisory board • Advisory board • Advisory board
Rajesh Gandhi	M	None	N/A
Stephen Gange	M	None	N/A
Edward Gardner	M	None	N/A
Thomas Giordano	M	None	N/A
David Glidden	M	• ViiV	• DSMB; Research support
Roy Gulick	C	None	N/A
Rohan Hazra	M	None	N/A
Charles Hicks	M	• Gilead • ViiV • Merck	• Consultant • Advisory board • Advisory board
Martin Hirsh	C	None	N/A
Tim Horn	M	None	N/A
Peter W. Hunt	M	• Merck • Gilead • ViiV	• Consultant • Consultant • Consultant
Rami Kantor	M	None	N/A
Andy Kayte	M	• BMS • CytoDyn • Theratechonologies • ViiV	• Honoraria • Honoraria • Honoraria • Travel support
Marla Keller	M	None	N/A

Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2016 to February 2017) (page 2 of 3)

Panel Member	Status	Company	Relationship
Michael Kozal	M	• Abbvie • Bristol-Myers Squibb • Gilead • Merck • Pfizer • ViiV • TiaMed	• Research support • Research support • Research support • Research support • Research support • Research support • Research support
H. Clifford Lane	C	None	N/A
Jeffrey Lennox	M	None	N/A
Henry Masur	M	None	N/A
Susanna Naggie	M	• Abbvie • BMS • Gilead • Janssen • Tacere	• Research support • Research support • Research support • Research support • Research support
Alice Pau	ES	None	N/A
Richard W. Price	M	• Merck	• Honoraria; Travel support
James Raper	M	None	N/A
David Reirden	M	None	N/A
Kimberly Scarsi	M	None	N/A
Adam Sherwat	M	None	N/A
Serena Spudich	M	None	N/A
Kimberly Struble	M	None	N/A
Susan Swindells	M	• Merck • ViiV	• Research support • Research support
Jeff Taylor	M	• Bristol-Myers Squibb	• Honoraria
Pablo Tebas	M	• Merck • GlaxoSmithKline • Gilead • Inivio • Sangamo • ViiV	• Research support; Consultant • Research support; Vaccine adjudication committee • Research support • Research support • Research support • Research support
Zelalem Temesgen	M	• Pfizer	• Research support

Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2016 to February 2017) (page 3 of 3)

Panel Member	Status	Company	Relationship
Melanie Thompson	M	• Bristol-Myers Squibb • CytoDyn, Inc. • Gilead • Merck • Pfizer • Roche Molecular Systems • Taimed • ViiV	• Research support • Research support • Research support • Research support • Research support • Research support • Research support • Research support
Phyllis Tien	M	None	N/A
Steven Vargas	M	• Gilead	• Advisory board
Rochelle Walensky	M	None	N/A

Key to Abbreviations: C = Co-Chair; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; M = Member; N/A = Not Applicable

* Research support = involvement in a pharmaceutical company sponsored trial in at least one of the following capacities:

- A member of the protocol development team
- A site PI
- Salary support for self

Introduction (Last updated January 28, 2016; last reviewed January 28, 2016)

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. In addition, ART is highly effective at preventing HIV transmission.[1] However, only 55% of people with HIV in the United States have suppressed viral loads,[2] mostly resulting from undiagnosed HIV infection and failure to link or retain diagnosed patients in care.

The 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 primary goal of the Panel is to provide HIV care practitioners with recommendations based on current knowledge of antiretroviral drugs (ARVs) 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 patients, ARV drugs or combinations to avoid, management of treatment failure, management of adverse effects and drug interactions, and special ART-related considerations in specific patient populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children to provide recommendations for adolescents at different stages of growth and development. Recommendations for ART regimens in these guidelines are most appropriate for postpubertal adolescents (i.e., sexual maturity rating [SMR] IV and V). Clinicians should follow recommendations in the Pediatric Guidelines when initiating ART in adolescents at SMR III or lower.[3] For recommendations related to pre- (PrEP) and post- (PEP) HIV exposure prophylaxis for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention (CDC).[4]

These guidelines represent current knowledge regarding the use of ARVs. 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 particular drugs or indications, and the use of the terms "safe" and "effective" may not be synonymous with the Food and Drug Administration (FDA)-defined legal standards for drug approval. The Panel frequently updates the guidelines (current and archived versions of the guidelines are available on the AIDS*info* website at http://www.aidsinfo.nih.gov). However, the guidelines cannot always be updated apace with the rapid evolution of new data and 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 (IRB)-approved clinical trials.

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 agents (ARVs) for the treatment of HIV in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 45 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), Food and Drug Administration (FDA), Health Resource 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 in HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open announcement to 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 for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf).
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. 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
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.
Other guidelines	These guidelines focus on antiretroviral therapy (ART) use for adults and adolescents with HIV. For more detailed discussion on the use of ART for children and prepubertal adolescents (SMR I – III), clinicians should refer to the Pediatric ARV Guidelines. These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women.
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 that may have an impact on the clinical care of patients. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the AIDS*info* website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommended 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).

Table 2. Rating Scheme for Recommendations

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

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., care for a larger panel of patients),[5-9] 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.

References

1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at https://www.ncbi.nlm.nih.gov/pubmed/21767103.
2. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2014. HIV Surveillance Supplemental Report. 2016;21(No. 4). Available at https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-21-4.pdf.
3. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.
4. Centers for Disease Control and Prevention; US Public Health Service. (2014). Pre-exposure prophylaxis for the prevention of HIV infection in the United States States—2014: a clinical practice guideline. Available at: http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf. Accessed [November 2, 2015].
5. Kitahata MM, Van Rompaey SE, Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *J Acquir Immune Defic Syndr*. Jun 1 2000;24(2):106-114. Available at https://www.ncbi.nlm.nih.gov/pubmed/10935685.
6. Landon BE, Wilson IB, McInnes K, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med*. May 23 2005;165(10):1133-1139. Available at https://www.ncbi.nlm.nih.gov/pubmed/15911726.
7. Kitahata MM, Van Rompaey SE, Dillingham PW, et al. Primary care delivery is associated with greater physician experience and improved survival among persons with AIDS. *J Gen Intern Med*. Feb 2003;18(2):95-103. Available at https://www.ncbi.nlm.nih.gov/pubmed/12542583.
8. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. *Antivir Ther*. Oct 2003;8(5):471-478. Available at https://www.ncbi.nlm.nih.gov/pubmed/14640395.

9. O'Neill M, Karelas GD, Feller DJ, et al. The HIV Workforce in New York State: Does Patient Volume Correlate with Quality? *Clin Infect Dis*. Dec 15 2015;61(12):1871-1877. Available at http://www.ncbi.nlm.nih.gov/pubmed/26423383.

Baseline Evaluation (Last updated May 1, 2014; last reviewed May 1, 2014)

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 the 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 to initiate care as recommended in HIV primary care guidelines[1] and guidelines for prevention and treatment of HIV-associated opportunistic infections.[2] The initial evaluation also should include discussion on the benefits of antiretroviral therapy (ART) for the patient's health and to prevent HIV transmission. Baseline information then can be used to define management goals and plans. In the case of previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete antiretroviral (ARV) history (including drug resistance testing results, if available), preferably through the review of past medical records. Newly diagnosed patients should also be asked about any prior use of ARV agents for prevention of HIV infection.

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

- HIV antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) **(AI)**;
- CD4 T lymphocyte cell count (CD4 count) **(AI)**;
- Plasma HIV RNA (viral load) **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN), and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses **(AIII)**;
- Fasting blood glucose and serum lipids **(AIII)**; and
- Genotypic resistance testing **(AII)**. For patients who have HIV RNA levels <500 to 1,000 copies/mL, viral amplification for resistance testing may not always be successful **(BII)**.

In addition, other tests (including screening tests for sexually transmitted infections and tests for determining the risk of opportunistic infections and need for prophylaxis) should be performed as recommended in HIV primary care and opportunistic infections guidelines.[1,2]

Patients living with HIV infection often must cope with many social, psychiatric, and medical issues that are best addressed through a patient-centered, multi-disciplinary approach to the disease. The baseline evaluation should include an evaluation of the patient's readiness for ART, including an assessment of high-risk behaviors, substance abuse, social support, mental illness, comorbidities, economic factors (e.g., unstable housing), 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 should also 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.

Education about HIV risk behaviors and effective strategies to prevent HIV transmission should be provided at each patient visit.

References

1. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the *HIV Med*icine Association of the Infectious Diseases Society of America.

Clin Infect Dis. Sep 1 2009;49(5):651-681. Available at https://www.ncbi.nlm.nih.gov/pubmed/19640227.

2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2017. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0.

Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy (Last updated October 17, 2017; last reviewed October 17, 2017)

Several laboratory tests are important for initial evaluation of patients with HIV upon entry into care, and 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 outlines the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations on the frequency of testing. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are routinely used to monitor patients with HIV: CD4 T lymphocyte (CD4) cell count to assess immune function and plasma HIV RNA (viral load) to assess level of HIV viremia. Resistance testing should be used to guide selection of an ARV regimen. 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. Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART and, if indicated, periodically after ART initiation, as treatment of these coinfections may affect the choice of ART. 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 Patients 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	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
HIV Serology	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√		√ During first 2 years of ART, or if viremia develops while patient is on ART, or CD4 count <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 monitoring is optional	√	√	√ Every 3–6 months
HIV Viral Load	√	√	√[d]	√[e]	√[e]		√	√	Repeat testing is optional
Resistance Testing	√	√[f]					√	√	√[f]
HLA-B*5701 Testing		√ If considering ABC							
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√	
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total) [g,h,i]	√	√ May repeat if patient is nonimmune and does not have chronic HBV infection[h]				√ May repeat if patient is nonimmune and does not have chronic HBV infection[h]		√ Including prior to starting HCV DAA (see HCV/HIV Infection)	

Laboratory Test	Timepoint or Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 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)[j]	√					√ Repeat HCV screening for at-risk patients[k]		√	
Basic Chemistry[l,m]	√	√	√	√				√	√ Every 6–12 months
ALT, AST, T. bilirubin	√	√	√	√				√	√ Every 6–12 months
CBC with Differential	√	√	√ If on ZDV	√ If on ZDV or if CD4 testing is done	√			√	√ Every 3–6 months
Fasting Lipid Profile[n]	√	√			√ If abnormal at last measurement	√ If normal at last measurement		√	√ If normal at baseline, annually
Fasting Glucose or Hemoglobin A1C	√	√		√ If abnormal at last measurement		√ If normal at last measurement		√	√ If normal at baseline, annually
Urinalysis[m,o]	√	√			√ If on TAF or TDF[l]	√		√	
Pregnancy Test		√ In women of child-bearing potential						√	

[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 Primary Care guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

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

[c] ART is indicated for all individuals 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] If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until viral load is suppressed to <200 copies/mL. Thereafter, repeat every 3 to 6 months.

[e] In patients on ART, viral load typically is measured every 3 to 4 months. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6-month intervals.

[f] Based on current rates of transmitted drug resistance to different ARV medications, 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 also test for resistance mutations to this class of drugs. In ART-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if resistance testing was performed at entry into care. In virologically suppressed patients who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; therefore, resistance testing should not be performed. Results from prior resistance testing can be helpful in constructing a new regimen.

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

[h] If HBsAg, HBsAb, and HBcAb are negative, hepatitis B vaccine series should be administered. Refer to HIV Primary Care and Opportunistic Infections guidelines for more detailed recommendations.[1,2]

[i] Most patients with isolated HBcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load for confirmation. If the HBV viral load is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If negative, the patient should be vaccinated. Refer to HIV Primary Care and the Adult and Adolescent Opportunistic Infections Guidelines for more detailed recommendations.[1,2]

[j] HCV antibody may not be adequate for screening in the setting of recent HCV infection (acquisition within 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.

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

[l] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting), and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TAF- or TDF-containing regimens.[3]

[m] Consult the *Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America* 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).

[n] Consult the National Lipid Association's recommendations for management of patients with dyslipidemia.[4]

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CD4 = CD4 T lymphocyte; Cl = chloride; FTC = emtricitabine; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO3 = bicarbonate; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the *HIV Med*icine association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):e1-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/24235263.
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2017. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0.
3. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the *HIV Med*icine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Nov 1 2014;59(9):e96-138. Available at http://www.ncbi.nlm.nih.gov/pubmed/25234519.
4. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*. Mar-Apr 2015;9(2):129-169. Available at http://www.ncbi.nlm.nih.gov/pubmed/25911072.

Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring (Last updated May 1, 2014; last reviewed May 1, 2014)

HIV RNA (viral load) and CD4 T lymphocyte (CD4) cell count are the two surrogate markers of antiretroviral treatment (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.

Measurement of CD4 count is particularly useful **before** initiation of ART. The CD4 cell count provides information on the overall immune function of a person with HIV. The measurement is critical in establishing thresholds for the initiation and discontinuation of opportunistic infection (OI) prophylaxis and in assessing the urgency to initiate ART.

The management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. In the United States, ART is now recommended for all patients with HIV regardless of their viral load or CD4 count **(AI)** (see Initiation of Antiretroviral Therapy). In the past, clinical practice, which was supported by treatment guidelines, was generally to monitor both CD4 cell count and viral load concurrently. However, because most patients with HIV in care now receive ART, the rationale for frequent CD4 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 **(AI)** and should be measured in all patients with HIV at entry into care **(AIII)**, at initiation of therapy **(AIII)**, and on a regular basis thereafter. For those patients who choose to delay therapy, 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 What to Start). 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 HIV-2 Infection.

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 generally as a viral load persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used). However, isolated blips (viral loads transiently detectable at low levels, typically HIV RNA <400 copies/mL) are not uncommon in successfully treated patients and are not 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 recent 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 a confirmed viral load >200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[10] (see Virologic Failure and Suboptimal Immunologic Response).

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 24 weeks after ART initiation; rarely, in some patients it

may take longer. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART or modification of therapy because of virologic failure.** Plasma viral load should be measured before initiation of ART and within 2 to 4 weeks but no later than 8 weeks after treatment initiation or modification **(AIII)**. The purpose of the measurements is to confirm an adequate initial 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 virologically suppressed patients in whom ART was modified 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 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 2 years and whose clinical and immunologic status is stable **(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, a number of additional 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 resistance testing to aid in the selection of an alternative regimen (see Drug-Resistance Testing and Virologic Failure and Suboptimal Immunologic Repsonse 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 subsequent 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 2 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 routinely 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 Opportunistic Infection Guidelines)[13] and the urgency to initiate ART **(AI)** (see the Initiating Antiretroviral Therapy section of these guidelines). 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 Opportunistic Infection Guidelines).[13] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 to 150 cells/mm^3 during the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 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 guidelines for treatment and prophylaxis of opportunistic infections.[13] In this setting, and in the first 2 years following ART initiation, CD4 count can be monitored at 3- to 6- month intervals **(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, 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 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 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 monitoring in the United States estimated that reducing CD4 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 regimen whose CD4 count has consistently ranged between 300 and 500 cells/mm^3 for at least 2 years, the Panel recommends CD4 monitoring on an annual basis **(BII)**. Continued CD4 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 cell count (e.g., interferon, chronic corticosteroids, or 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)** (see Virologic Failure and Suboptimal Immunologic Response).

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 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. Alpha-interferon may reduce the absolute CD4 count without changing the CD4 percentage.[27] In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.

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[b] **(AIII)**
After initiating ART	Preferably within 2 to 4 weeks (and no later than 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 2 to 4 weeks (and no later than 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 every 3 months or more frequently if indicated **(AIII)**.	Every 3 to 6 months **(AI)**
During the first 2 years of ART	Every 3 to 4 months **(AIII)**	Every 3 to 6 months[a] **(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)		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 interferon, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months **(AIII)**	Perform CD4 count and repeat as clinically indicated[c] **(AIII)**

[a] Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended **(BIII)**.

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

[c] 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 infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.

References

1. Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS*. May 7 1999;13(7):797-804. Available at https://www.ncbi.nlm.nih.gov/pubmed/10357378.
2. Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis*. Jan 1998;177(1):40-47. Available at https://www.ncbi.nlm.nih.gov/pubmed/9419168.

3. Thiebaut R, Morlat P, Jacqmin-Gadda H, et al. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. Groupe d'Epidemiologie du SIDA en Aquitaine (GECSA). *AIDS*. May 26 2000;14(8):971-978. Available at https://www.ncbi.nlm.nih.gov/pubmed/10853978.
4. Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: a meta-analysis. HIV Surrogate Marker Collaborative Group. *AIDS Res Hum Retroviruses*. Aug 10 2000;16(12):1123-1133. Available at http://www.ncbi.nlm.nih.gov/pubmed/10954887.
5. Havlir DV, Bassett R, Levitan D, et al. Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA*. Jul 11 2001;286(2):171-179. Available at https://www.ncbi.nlm.nih.gov/pubmed/11448280.
6. Damond F, Roquebert B, Benard A, et al. Human immunodeficiency virus type 1 (HIV-1) plasma load discrepancies between the Roche COBAS AMPLICOR HIV-1 MONITOR Version 1.5 and the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assays. *J Clin Microbiol*. Oct 2007;45(10):3436-3438. Available at https://www.ncbi.nlm.nih.gov/pubmed/17715371.
7. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis*. Jan 15 2009;48(2):260-262. Available at https://www.ncbi.nlm.nih.gov/pubmed/19113986.
8. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr*. Aug 1 2010;54(4):442-444. Available at https://www.ncbi.nlm.nih.gov/pubmed/20611035.
9. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. Nov 2013;57(10):1489-1496. Available at http://www.ncbi.nlm.nih.gov/pubmed/23946221.
10. Ribaudo H, Lennox J, Currier J, al e. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada.
11. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. Jun 15 1997;126(12):946-954. Available at https://www.ncbi.nlm.nih.gov/pubmed/9182471.
12. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*. Jul 13 2002;360(9327):119-129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12126821.
13. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the *HIV Med*icine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed January 6, 2014.
14. Mocroft A, Furrer HJ, Miro JM, et al. The incidence of AIDS-defining illnesses at a current CD4 count >/= 200 cells/muL in the post-combination antiretroviral therapy era. *Clin Infect Dis*. Oct 2013;57(7):1038-1047. Available at http://www.ncbi.nlm.nih.gov/pubmed/23921881.
15. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med*. Oct 13 2003;163(18):2187-2195. Available at https://www.ncbi.nlm.nih.gov/pubmed/14557216.
16. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. Feb 1 2007;44(3):441-446. Available at https://www.ncbi.nlm.nih.gov/pubmed/17205456.
17. Palella FJ, Jr., Armon C, Chmiel JS, et al. CD4 cell count at initiation of ART, long-term likelihood of achieving CD4 >750 cells/mm3 and mortality risk. *J Antimicrob Chemother*. Sep 2016;71(9):2654-2662. Available at https://www.ncbi.nlm.nih.gov/pubmed/27330061.
18. Althoff KN, Justice AC, Gange SJ, et al. Virologic and immunologic response to HAART, by age and regimen class. *AIDS*. Oct 23 2010;24(16):2469-2479. Available at http://www.ncbi.nlm.nih.gov/pubmed/20829678.
19. Gale HB, Gitterman SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts >=300 cells/muL and HIV-1 suppression? *Clin Infect Dis*. May 2013;56(9):1340-1343. Available at http://www.ncbi.nlm.nih.gov/pubmed/23315315.
20. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS*. Nov 13 2013;27(17):2759-2763. Available at http://www.

ncbi.nlm.nih.gov/pubmed/23842127.

21. Costiniuk CT, Fergusson DA, Doucette S, Angel JB. Discontinuation of Pneumocystis jirovecii pneumonia prophylaxis with CD4 count <200 cells/microL and virologic suppression: a systematic review. *PLoS One*. 2011;6(12):e28570. Available at http://www.ncbi.nlm.nih.gov/pubmed/22194853.
22. Helleberg M, Kronborg G, Larsen CS, et al. CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. *Clin Infect Dis*. Jul 2013;57(2):314-321. Available at http://www.ncbi.nlm.nih.gov/pubmed/23575194.
23. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med*. Oct 14 2013;173(18):1746-1748. Available at http://www.ncbi.nlm.nih.gov/pubmed/23978894.
24. Zurlo JJ, Wood L, Gaglione MM, Polis MA. Effect of splenectomy on T lymphocyte subsets in patients infected with the human immunodeficiency virus. *Clin Infect Dis*. Apr 1995;20(4):768-771. Available at https://www.ncbi.nlm.nih.gov/pubmed/7795071.
25. Bernard NF, Chernoff DN, Tsoukas CM. Effect of splenectomy on T-cell subsets and plasma HIV viral titers in HIV-infected patients. *J Hum Virol*. Jul-Aug 1998;1(5):338-345. Available at https://www.ncbi.nlm.nih.gov/pubmed/10195261.
26. Casseb J, Posada-Vergara MP, Montanheiro P, et al. T CD4+ cells count among patients co-infected with human immunodeficiency virus type 1 (HIV-1) and human T-cell leukemia virus type 1 (HTLV-1): high prevalence of tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). *Rev Inst Med Trop Sao Paulo*. Jul-Aug 2007;49(4):231-233. Available at https://www.ncbi.nlm.nih.gov/pubmed/17823752.
27. Berglund O, Engman K, Ehrnst A, et al. Combined treatment of symptomatic human immunodeficiency virus type 1 infection with native interferon-alpha and zidovudine. *J Infect Dis*. Apr 1991;163(4):710-715. Available at https://www.ncbi.nlm.nih.gov/pubmed/1672701.

Drug-Resistance Testing (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations

For Antiretroviral Therapy-Naive Persons:

- HIV drug-resistance testing is recommended for persons with HIV at entry into care to guide selection of the initial antiretroviral therapy (ART) regimen **(AII)**. If therapy is deferred, repeat testing may be considered at the time of ART initiation **(CIII)**.
- Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients **(AIII)**.
- In special circumstances (e.g., in persons with acute or recent [early] HIV infection and in pregnant women with HIV), 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 (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes INSTI genotype testing **(BIII)**.

For Antiretroviral Therapy-Experienced Persons:

- HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ART regimens in the following patients:
  - In persons with virologic failure and HIV RNA levels >1,000 copies/mL **(AI)**.
  - In persons with HIV RNA levels >500 copies/mL but <1,000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered **(BII)**.
  - Drug-resistance testing should also be performed when managing suboptimal viral load reduction **(AII)**.
- When a person with HIV experiences virologic failure while receiving an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include a drug from this class in subsequent regimens **(AII)**.
- Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy **(AII)**. If more than 4 weeks have elapsed since the ARVs 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 **(CIII)**.
- Genotypic testing is recommended as the preferred resistance testing to guide therapy in persons with suboptimal virologic response or virologic failure while on first- or second-line regimens **(AII)**.
- The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns **(BIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

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. Clinicians should check with the testing laboratory. INSTI-resistance testing is particularly important in persons who experience virologic failure while taking an INSTI-containing regimen. Testing for fusion inhibitor resistance can also be ordered separately. Co-receptor tropism assays should be performed when considering the use of a CCR5 antagonist. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available (see Co-receptor Tropism Assays).

Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes. Most genotypic assays involve sequencing the reverse transcriptase (RT), protease (PR), and integrase (IN) genes 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 (see http://www.iasusa.org/resistance_mutations).[1] The Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu) also provides helpful guidance for interpreting genotypic resistance test results. Various tools to assist the provider in interpreting genotypic test results are now available.[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 optimal new regimens.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT and PR gene sequences and, more recently, integrase and envelope 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 is 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 are now available 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 less than 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 drugs that exert selective pressure on drug-resistant populations are discontinued. As a consequence, the proportion of virus with resistance mutations decreases to below the 10% to 20% threshold.[12-14] In the case of some drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. 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, resistance testing is most valuable when performed while a person is taking ARV drugs or, if that is not possible, then within 4 weeks after discontinuing therapy **(AII)**. Because resistant virus may persist longer in the plasma of some patients, resistance testing done 4 to 6 weeks after discontinuation of drugs may still detect mutations. However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens.

Use of Resistance Assays in Clinical Practice (See Table 5)

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 antiretroviral therapy (ART).[16-19] The risk of acquiring drug-resistant virus is related to

the prevalence of drug resistance in people with HIV engaging in high-risk behaviors in a given community. In high-income countries (e.g., the United States, some European countries, Australia, and Japan), approximately 10% to 17% of ART-naive individuals have resistance mutations to at least one ARV drug.[20] Up to 8%, but generally less than 5%, of transmitted viruses will exhibit resistance to drugs from more than 1 class.[20-23] Transmitted resistant HIV is generally either NRTI- or NNRTI-resistant. PI resistance is much less common, and to date, transmitted INSTI resistance is rare.[24]

In persons with acute or recent (early) HIV infection, resistance testing can guide therapy selection to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AII)**. A genotypic assay is preferred for this purpose **(AIII)**. In this setting, treatment initiation should not be delayed pending resistance testing results if the individual is willing and able to begin treatment. Once results are reported, the regimen can be modified if warranted (see Acute and Recent HIV (Early) 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.[25-27] Therefore, if ART is deferred, resistance testing should still be performed during acute HIV infection **(AIII)**. In this situation, the genotypic resistance test result may be kept on record until the person begins ART. Repeat resistance testing at the start of treatment may be considered because a patient may acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART **(CIII)**.

Interpretation of drug-resistance testing before ART initiation in persons with chronic HIV infection is less straightforward. 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.[28-30] No prospective trial has addressed whether drug-resistance testing before initiation of therapy confers benefit in this population. However, data from several studies suggest that virologic responses in persons with baseline resistance mutations are suboptimal.[16-19,31-33] In addition, an analysis of early genotypic resistance testing in ARV-naive persons suggests that baseline testing in this population is cost effective and should be performed.[34] Therefore, resistance testing in people with chronic infections 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, more rapid turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and test results that are easier to interpret **(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)**.

Standard genotypic drug-resistance testing in ARV-naive persons 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 may also increase. Therefore, when INSTI resistance is suspected, providers should supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs **(BIII)**.

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 assessed the utility of resistance testing to guide ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6,35-41] In general, these studies found that changes in therapy based on resistance testing 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 performance of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.[42] Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV

regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)** (see Virologic Failure). In persons with HIV RNA >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Drug-resistance testing in persons with a plasma viral load <500 copies/mL is not usually recommended because resistance assays cannot be consistently performed given low HIV RNA levels **(AIII)**.

Resistance testing can also help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination ART is, for certain patients, associated with resistance to only one component of the regimen.[43-45] In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

Genotypic testing is generally preferred for resistance testing in patients who are on a first or second ARV drug regimen and experiencing virologic failure or suboptimal viral load reduction **(AII)**. 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 ART regimens.[46] In patients who experience virologic failure while on INSTI-based regimens, 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 persons with known or suspected complex drug-resistance mutation patterns **(BIII)**.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)**. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co receptor use is now commercially available and is less expensive than phenotypic assays. Evaluation of genotypic assays is ongoing, but current data suggest that genotypic tropism testing should be considered as an alternative to phenotypic tropism testing. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist.[47] Resistance to CCR5 antagonists in the absence of detectable CXCR4-using virus has been reported, but such resistance is uncommon (see Co-receptor Tropism Assays).

A next-generation sequencing genotypic resistance assay, which analyzes HIV-1 pro-viral DNA in the host cells, is now commercially available. This test aims to detect archived resistance mutations in patients with HIV RNA below the limit of detection. However, the clinical utility of this assay has yet to be determined.

Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to maximally reduce plasma HIV RNA to provide optimal maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant women with HIV before initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Phenotypic testing in those found to have complex drug-resistance mutation patterns may provide additional information **(BIII)**. Optimal prevention of perinatal transmission requires initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting and Recommendation	Rationale
Drug-Resistance Assay Recommended	
In acute or recent (early) HIV infection: 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)**. If ART is deferred, repeat resistance testing may be considered when therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified 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. Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART **(AII)**. A genotypic assay is generally preferred **(AIII)**. If an INSTI is considered for an ART-naive patient and transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay **(BIII)**. If therapy is deferred, repeat resistance testing may be considered before initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**. If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).	Transmitted HIV with baseline resistance to at least 1 drug is seen in 10% to 17% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated patients with chronic HIV infection. 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. 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.
In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered **(BII)**. A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens **(AII)**. When virologic failure occurs while a patient is on an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**. If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays). Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**.	Drug-resistance testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy **(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. 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). Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns, particularly to PIs.
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 and thus help the clinician identify the number of active drugs available for a new regimen.

Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting and Recommendation	Rationale
Drug-Resistance Assay Recommended	
In pregnant women with HIV: Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in pregnant women with HIV is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal 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.
Drug-Resistance Assay Not Usually Recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued **(BIII)**.	Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor

References

1. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. Jul 15 2008;47(2):266-285. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18549313.
2. Flandre P, Costagliola D. On the comparison of artificial network and interpretation systems based on genotype resistance mutations in HIV-1-infected patients. *AIDS*. Oct 24 2006;20(16):2118-2120. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17053360.
3. Vercauteren J, Vandamme AM. Algorithms for the interpretation of HIV-1 genotypic drug resistance information. *Antiviral Res*. Sep 2006;71(2-3):335-342. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16782210.
4. Gianotti N, Mondino V, Rossi MC, et al. Comparison of a rule-based algorithm with a phenotype-based algorithm for the interpretation of HIV genotypes in guiding salvage regimens in HIV-infected patients by a randomized clinical trial: the mutations and salvage study. *Clin Infect Dis*. May 15 2006;42(10):1470-1480. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16619162.
5. Torti C, Quiros-Roldan E, Regazzi M, et al. A randomized controlled trial to evaluate antiretroviral salvage therapy guided by rules-based or phenotype-driven HIV-1 genotypic drug-resistance interpretation with or without concentration-controlled intervention: the Resistance and Dosage Adapted Regimens (RADAR) study. *Clin Infect Dis*. Jun 15 2005;40(12):1828-1836. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15909273.
6. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS*. Jan 25 2002;16(2):209-218. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11807305.
7. Lanier ER, Ait-Khaled M, Scott J, et al. Antiviral efficacy of abacavir in antiretroviral therapy-experienced adults harbouring HIV-1 with specific patterns of resistance to nucleoside reverse transcriptase inhibitors. *Antivir Ther*. Feb 2004;9(1):37-45. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15040535.
8. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. *J Infect Dis*. Mar 1 2004;189(5):837-846. Available

at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14976601.

9. Flandre P, Chappey C, Marcelin AG, et al. Phenotypic susceptibility to didanosine is associated with antiviral activity in treatment-experienced patients with HIV-1 infection. *J Infect Dis*. Feb 1 2007;195(3):392-398. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17205478.
10. Naeger LK, Struble KA. Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. *AIDS*. Jan 11 2007;21(2):179-185. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17197808.
11. Naeger LK, Struble KA. Effect of baseline protease genotype and phenotype on HIV response to atazanavir/ritonavir in treatment-experienced patients. *AIDS*. Apr 4 2006;20(6):847-853. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16549968.
12. Verhofstede C, Wanzeele FV, Van Der Gucht B, De Cabooter N, Plum J. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS*. Dec 24 1999;13(18):2541-2546. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10630523.
13. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. Dec 22 2000;14(18):2857-2867. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153667.
14. Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS*. Dec 24 1999;13(18):F123-127. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10630517.
15. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. *J Infect Dis*. Nov 1 2006;194(9):1309-1318. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17041858.
16. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med*. Aug 8 2002;347(6):385-394. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12167680.
17. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses*. Aug 2007;23(8):988-995. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17725415.
18. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. *J Acquir Immune Defic Syndr*. Dec 15 2006;43(5):535-540. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17057609.
19. Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis*. Mar 15 2008;197(6):867-870. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18269317.
20. World Health Organization. WHO HIV Drug Resistance Report 2012. Geneva, Switzerland. Available at http://www.who.int/hiv/pub/drugresistance/report2012. Accessed May 13, 2016.
21. Yanik EL, Napravnik S, Hurt CB, et al. Prevalence of transmitted antiretroviral drug resistance differs between acutely and chronically HIV-infected patients. *J Acquir Immune Defic Syndr*. Oct 1 2012;61(2):258-262. Available at http://www.ncbi.nlm.nih.gov/pubmed/22692092.
22. Agwu AL, Bethel J, Hightow-Weidman LB, et al. Substantial multiclass transmitted drug resistance and drug-relevant polymorphisms among treatment-naive behaviorally HIV-infected youth. *AIDS Patient Care STDS*. Apr 2012;26(4):193-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/22563607.
23. Castor D, Low A, Evering T, et al. Transmitted drug resistance and phylogenetic relationships among acute and early HIV-1-infected individuals in New York City. *J Acquir Immune Defic Syndr*. Sep 1 2012;61(1):1-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/22592583.
24. Doyle T, Dunn DT, Ceccherini-Silberstein F, et al. Integrase inhibitor (INI) genotypic resistance in treatment-naive and raltegravir-experienced patients infected with diverse HIV-1 clades. *J Antimicrob Chemother*. Nov 2015;70(11):3080-

3086. Available at http://www.ncbi.nlm.nih.gov/pubmed/26311843.

25. Johnson JA, Li JF, Wei X, et al. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naive populations and associate with reduced treatment efficacy. *PLoS Med*. Jul 29 2008;5(7):e158. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18666824.
26. Simen BB, Simons JF, Hullsiek KH, et al. Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. *J Infect Dis*. Mar 1 2009;199(5):693-701. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19210162.
27. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. Mar 2010;201(5):662-671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20102271.
28. Smith DM, Wong JK, Shao H, et al. Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. *J Infect Dis*. Aug 1 2007;196(3):356-360. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17597449.
29. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis*. Feb 1 2005;40(3):468-474. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15668873.
30. Little SJ, Frost SD, Wong JK, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *J Virol*. Jun 2008;82(11):5510-5518. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18353964.
31. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*. Jul 14 2004;292(2):180-189. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15249567.
32. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med*. Jul 15 2004;351(3):229-240. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15247339.
33. Pillay D, Bhaskaran K, Jurriaans S, et al. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. *AIDS*. Jan 2 2006;20(1):21-28. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327315.
34. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis*. Nov 1 2005;41(9):1316-1323. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16206108.
35. Cingolani A, Antinori A, Rizzo MG, et al. Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS*. Feb 15 2002;16(3):369-379. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11834948.
36. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet*. Jun 26 1999;353(9171):2195-2199. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10392984.
37. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS*. 2000;14(9):F83-93. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10894268&dopt=Abstract.
38. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS*. Mar 8 2002;16(4):579-588. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11873001.
39. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. *AIDS*. Mar 29 2002;16(5):727-736. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11964529.
40. Vray M, Meynard JL, Dalban C, et al. Predictors of the virological response to a change in the antiretroviral treatment regimen in HIV-1-infected patients enrolled in a randomized trial comparing genotyping, phenotyping and standard of

care (Narval trial, ANRS 088). *Antivir Ther*. Oct 2003;8(5):427-434. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14640390.

41. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis*. Mar 1 2004;38(5):723-730. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14986258.
42. Palella FJ, Jr., Armon C, Buchacz K, et al. The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: a cohort study. *Ann Intern Med*. Jul 21 2009;151(2):73-84. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19620160.
43. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. Jan 12 2000;283(2):229-234. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634339.
44. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072 Study Team). *JAMA*. Jan 12 2000;283(2):205-211. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634336.
45. Machouf N, Thomas R, Nguyen VK, et al. Effects of drug resistance on viral load in patients failing antiretroviral therapy. *J Med Virol*. May 2006;78(5):608-613. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16555280.
46. Anderson JA, Jiang H, Ding X, et al. Genotypic susceptibility scores and HIV type 1 RNA responses in treatment-experienced subjects with HIV type 1 infection. *AIDS Res Hum Retroviruse*s. May 2008;24(5):685-694. Available at http://www.ncbi.nlm.nih.gov/pubmed/18462083.
47. Lewis M MJ, Simpson P, et al. Changes in V3 loop sequence associated with failure of maraviroc treatment in patients enrolled in the MOTIVATE 1 and 2 trials. Presented at: 15th Conference on Retroviruses and Opportunistic Infections. 2008. Boston, Massachusetts.

Co-Receptor Tropism Assays (Last updated February 12, 2013; last reviewed February 12, 2013)

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 also recommended for patients with HIV who exhibit virologic failure while 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)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***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 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, to a lesser degree, genotypic assays have been developed that can determine or predict the co-receptor tropism (i.e., CCR5, CXCR4, or both) 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, a genotypic assay to predict co-receptor usage is also now 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. Viruses in many untreated persons with HIV eventually exhibit a shift in co-receptor tropism from CCR5 usage to either CXCR4 or both CCR5 and CXCR4 tropism (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts,[3,4] but whether this tropism shift is a cause or a consequence of progressive immunodeficiency remains undetermined.[1] Antiretroviral (ARV)-treated patients with extensive drug resistance are more likely to harbor X4- or D/M-tropic variants than untreated patients with comparable CD4 counts.[5] The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3.[5,6]

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.[7,8] 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, participants with HIV enrolled in pre-marketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the *Trofile* assay.[8] This earlier assay failed to routinely detect the presence of low levels of CXCR4 utilizing variants. As a consequence, some participants enrolled in these clinical trials harbored low levels of CXCR4 utilizing virus at baseline that were below the assay limit of detection and exhibited rapid virologic failure after initiation of a CCR5 antagonist.[9] The assay has been revised 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.[10] Although this more sensitive

assay has had limited use in prospective clinical trials, it is now the only one 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 plasma HIV-1 RNA below the limit of detection, co-receptor usage can be determined from proviral DNA obtained from peripheral blood mononuclear cells; however, the clinical utility of this assay remains to be determined.[11]

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. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50%–70%) for the presence of a CXCR4-utilizing virus. Given these performance characteristics, these assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant.[12]

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.[13-15] On the basis of these data, accessibility, and cost, European guidelines currently favor genotypic testing to determine co-receptor usage.[16] An important caveat to these results 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.

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)**. 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 while on a CCR5 antagonist **(BIII)**. Virologic failure also may 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 usefulness. Therefore, a phenotypic test for co-receptor usage is generally preferred **(AI)**. However, because phenotypic testing is more expensive and requires more time to perform, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test **(BII)**.

A tropism assay may potentially be used in clinical practice for prognostic purposes or to assess tropism before starting ART if future use of a CCR5 antagonist is anticipated (e.g., a regimen change for toxicity). Currently, sufficient data do not exist to support these uses.

References

1. Moore JP, Kitchen SG, Pugach P, Zack JA. The CCR5 and CXCR4 coreceptors—central to understanding the transmission and pathogenesis of human immunodeficiency virus type 1 infection. *AIDS Res Hum Retroviruses*. 2004;20(1):111-126. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15000703.
2. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. *Nat Med*. 2005;11(11):1170-1172. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16205738.
3. Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. Change in coreceptor use correlates with disease progression in HIV-1-infected individuals. *J Exp Med*. 1997;185(4):621-628. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9034141.
4. Koot M, Keet IP, Vos AH, et al. Prognostic value of HIV-1 syncytium-inducing phenotype for rate of CD4+ cell

entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8096374.

5. Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis*. 2006;194(7):926-930. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16960780.
6. Wilkin TJ, Su Z, Kuritzkes DR, et al. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. *Clin Infect Dis*. 2007;44(4):591-595. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17243065.
7. Trouplin V, Salvatori F, Cappello F, et al. Determination of coreceptor usage of human immunodeficiency virus type 1 from patient plasma samples by using a recombinant phenotypic assay. *J Virol*. 2001;75(1):251-259. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11119595.
8. Whitcomb JM, Huang W, Fransen S, et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. *Antimicrob Agents Chemother*. 2007;51(2):566-575. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17116663.
9. Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. *J Virol*. 2006;80(10):4909-4920. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16641282.
10. Trinh L, Han D, Huang W, et al. Technical validation of an enhanced sensitivity Trofile HIV coreceptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5. *Antivir Ther*. 2008;13(Suppl 3):A128
11. Toma J, Frantzell A, Cook J, et al. Phenotypic determination of HIV-1 coreceptor tropism using cell-associated DNA derived from blood samples. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; 2010; San Francisco, CA.
12. Lin NH, Kuritzkes DR. Tropism testing in the clinical management of HIV-1 infection. *Curr Opin HIV AIDS*. 2009;4(6):481-487. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20048714.
13. McGovern RA, Thielen A, Mo T, et al. Population-based V3 genotypic tropism assay: a retrospective analysis using screening samples from the A4001029 and MOTIVATE studies. *AIDS*. 2010;24(16):2517-2525. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20736814.
14. McGovern RA, Thielen A, Portsmouth S, et al. Population-based sequencing of the V3-loop can predict the virological response to maraviroc in treatment-naive patients of the MERIT trial. *J Acquir Immune Defic Syndr*. 2012;61(3):279-286. Available at http://www.ncbi.nlm.nih.gov/pubmed/23095934.
15. Archer J, Weber J, Henry K, et al. Use of four next-generationsequencing platforms to determine HIV-1 coreceptor tropism. *PLoS One*. 2012;7(11):e49602. Available at http://www.ncbi.nlm.nih.gov/pubmed/23166726.
16. Vandekerckhove LP, Wensing AM, Kaiser R, et al. European guidelines on the clinical management of HIV-1 tropism testing. *Lancet Infect Dis*. 2011;11(5):394-407. Available at http://www.ncbi.nlm.nih.gov/pubmed/21429803.

HLA-B*5701 Screening (Last updated December 1, 2007; last 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 = Optional*
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)**.

References

1. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001;23(10):1603-1614.
2. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359(9308):727-732.
3. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002;359(9312):1121-1122.
4. Phillips EJ, Sullivan JR, Knowles SR, et al. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. *AIDS*. 2002;16(16):2223-2225.
5. Phillips E, Rauch A, Nolan D, et al. Pharmacogenetics and clinical characteristics of patch test confirmed patients with abacavir hypersensitivity. *Rev Antivir Ther*. 2006:3: Abstract 57.
6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118.

Treatment Goals (Last updated January 28, 2016; last 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 the Continuum of Care).

References

1. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. Jul 15 2010;363(3):257-265. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20647201.

2. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. Jul 20 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.

3. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.

4. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. Apr 30 2009;360(18):1815-1826. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19339714.

5. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. Aug 5 1999;341(6):385-393. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10432323.

6. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ*. 2009;338:b1649. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19406887.

7. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21767103.

8. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. Feb 20 2011;25(4):473-477. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160416.

9. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med*. Feb 15 1996;334(7):426-431. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8552144.

10. Garcia F, de Lazzari E, Plana M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr*. Jun 1 2004;36(2):702-713. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15167289.

11. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. Nov 30 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.

Initiation of Antiretroviral Therapy (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection **(AI)**. • ART is also recommended for individuals with HIV to prevent HIV transmission **(AI)**. • When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
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

Without antiretroviral therapy (ART), most individuals with HIV will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and leading to AIDS-defining illnesses and premature death. The primary goal of ART is to prevent HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication to sustain plasma HIV-1 RNA (viral load) below limits of quantification by 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 prolongs life.

Furthermore, high plasma HIV-1 RNA is a major risk factor for HIV transmission; effective ART can reduce both viremia and transmission of HIV to sexual partners.[1,2] Modelling studies suggest that expanded use of ART may lower incidence and, eventually, prevalence of HIV on a community or population level.[3] Thus, a secondary goal of ART is to reduce the risk of HIV transmission.

Historically, individuals with HIV have had low CD4 counts at presentation to care.[4] However, there have been concerted efforts to increase testing of at-risk individuals and to link individuals with HIV to medical care before they have advanced HIV disease. Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining and certain serious non-AIDS 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 never achieve CD4 counts >500 cells/mm^3 after up to 10 years on ART[5,6] and have a shorter life expectancy than those initiating therapy at higher CD4 count thresholds.[5-7]

Two large, randomized controlled trials that addressed the optimal time to initiate ART—START[8] and TEMPRANO[9]—demonstrated approximately a 50% reduction in morbidity and mortality among individuals with HIV who had CD4 counts >500 cells/mm^3 and who were randomized to receive ART immediately versus delaying initiation of ART (described in more detail below). The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) therefore recommends immediate initiation of ART for all people living with HIV, regardless of CD4 count **(AI)**. Prompt initiation of ART is particularly important for patients with certain clinical conditions, as discussed below.

The decision to initiate ART should always include consideration of a patient's comorbid conditions and his or her willingness and readiness to initiate therapy. Thus, on a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible.

Panel's Recommendations

ART is recommended for all individuals with HIV, regardless of CD4 cell count, to reduce the morbidity and

mortality associated with HIV infection **(AI)**. ART is also recommended for individuals with HIV to prevent HIV transmission **(AI)**. When initiating ART, it is important to educate patients about the benefits of ART, and to address barriers to adherence and recommend strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible. 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.

While ART is recommended for all patients, the following conditions increase the urgency to initiate therapy:

- Pregnancy (refer to the Perinatal Guidelines for more detailed recommendations on the management of pregnant women with HIV)[10]
- AIDS-defining conditions, including HIV-associated dementia (HAD) and AIDS-associated malignancies
- Acute opportunistic infections (OIs) (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm^3)
- HIV-associated nephropathy (HIVAN)
- Acute/early infection (see discussion in the Acute/Early Infection section)
- HIV/hepatitis B virus coinfection
- HIV/hepatitis C virus coinfection

Acute Opportunistic Infections and Malignancies

In patients who have AIDS-associated opportunistic diseases for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy), improvement of immune function with ART may improve disease outcomes, thus ART should be started as soon as possible. For patients with mild to moderate cutaneous Kaposi's sarcoma (KS), prompt initiation of ART alone without chemotherapy has been associated with improvement of the KS lesions, even though initial transient progression of KS lesions as a manifestation of immune reconstitution inflammatory syndrome (IRIS) can also occur.[11] Similarly, although an IRIS-like presentation of non-Hodgkin's lymphoma after initiation of ART has been described,[12] greater ART-mediated viral suppression is also associated with longer survival among individuals undergoing treatment for AIDS lymphoma.[13] Drug interactions should be considered when selecting ART given the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some non-nucleoside reverse transcriptase inhibitors [NNRTIs] and ritonavir- or cobicistat-boosted regimens). However, a diagnosis of malignancy should not delay initiation of ART nor should initiation of ART delay treatment for the malignancy.

In the setting of some OIs, such as cryptococcal and tuberculous meningitis, for which immediate ART may increase the risk of serious IRIS, a short delay before initiating ART may be warranted.[14-17] When ART is initiated in a patient with an intracranial infection, the patient should be closely monitored for signs and symptoms associated with IRIS. In the setting of other OIs, such as *Pneumocystis jirovecii* pneumonia, early initiation of ART is associated with increased survival;[18] therefore, ART should not be delayed.

In patients who have active non-meningeal tuberculosis, initiating ART during treatment for tuberculosis confers a significant survival advantage;[19-23] therefore, ART should be initiated as recommended in *Mycobacterium Tuberculosis* Disease with HIV Coinfection.

Clinicians should refer to the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[11] for more detailed discussion on when to initiate ART in the setting of a specific OI.

The Need for Early Diagnosis of HIV

Fundamental to the earlier initiation of ART recommended in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. Unfortunately, in some patients, HIV infection is not diagnosed until the later stages of the disease. Despite the recommendations for routine, opt-out HIV screening in the health care setting regardless of perceptions about a patient's risk of infection[24] and the gradual increase in CD4 counts at first presentation to care, the median CD4 count of newly diagnosed patients remains below 350 cells/mm^3.[4] Diagnosis of HIV infection is delayed more often in nonwhites, those who use injection drugs, and older adults than in other populations, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[25-27] Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current Centers for Disease Control and Prevention recommendations is essential. It is also critical that all patients who receive an HIV diagnosis are educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. Once patients are in care, focused effort is required to initiate ART and retain them in the health care system so that both the individuals with HIV and their sexual partners can fully benefit from early diagnosis and treatment (see Adherence to the Continuum of Care).

Evidence Supporting Benefits of Antiretroviral Therapy to Prevent Morbidity and Mortality

Although observational studies had been inconsistent in defining the optimal time to initiate ART,[28-31] randomized controlled trials now definitively demonstrate that ART should be initiated in all patients with HIV, regardless of disease stage. The urgency to initiate ART is greatest for patients at lower CD4 counts, where the absolute risk of OIs, non-AIDS morbidity, and death is highest. Randomized controlled trials have long shown that ART improves survival and delays disease progression in patients with CD4 counts <200 cells/mm^3 and/or history of AIDS-defining conditions.[18,32] Additionally, a randomized controlled trial conducted in Haiti showed that patients who started ART with CD4 counts between 200 to 350 cells/mm^3 survived longer than those who deferred ART until their CD4 counts fell below 200 cells/mm^3.[33] Most recently, the published START and TEMPRANO trials provide the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 cell count **(AI)**. The results of these two studies are summarized below.

The START trial is a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm^3 were randomized to initiate ART soon after randomization (immediate-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. When the randomized arms of the study were closed, the primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events/100 person-years) in the immediate ART arm and 96 participants (4.1%, or 1.38 events/100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART [95% confidence interval (CI), 0.30–0.62, $P < .001$]). The most common clinical events reported were tuberculosis and AIDS and non-AIDS malignancies. The majority (59%) of clinical events in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm^3, evidence for a benefit of immediate ART even before CD4 count declines below this threshold. Furthermore, the benefit of immediate ART was evident across all participant subgroups examined, including men and women, older and younger participants, individuals with high and low plasma HIV RNA levels, and participants living in high-income and low/middle-income countries. Although START was not sufficiently powered to examine the benefit of immediate ART for each category of clinical events, the benefit of immediate ART appeared to be particularly strong for AIDS events (HR 0.28, [95% CI, 0.15–0.50, $P < .001$]), tuberculosis (HR 0.29, [95% CI, 0.12–0.73, $P = .008$]), and malignancies (HR 0.36, [95% CI, 0.19 to 0.66; $P = .001$]). Importantly, immediate ART also significantly reduced the rate of pooled serious non-AIDS events (HR0.61, [95% CI, 0.38–0.97, $P = 0.04$]).[8]

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm^3 were randomized

to either immediate ART or deferred ART (based on the national guidelines criteria for starting treatment); half of the participants in each group received isoniazid for prevention of tuberculosis 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 with immediate ART than with deferred ART, with a hazard ratio of 0.56 in favor of early ART (CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART is beneficial in reducing the rate of these clinical events.[9]

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

Theoretical Continued Benefit of Early Antiretroviral Therapy Initiation Long After Viral Suppression is Achieved

While the START and TEMPRANO studies demonstrated a clear benefit of immediate ART initiation in individuals with CD4 cell counts >500 cells/mm^3, it is plausible that the benefits of early ART initiation continue long after viral suppression is achieved. As detailed in the Poor CD4 Cell Recovery and Persistent Inflammation section, persistently low CD4 counts and abnormally high levels of immune activation and inflammation despite suppressive ART predict an increased risk of not only AIDS events, but also non-AIDS events including kidney disease, liver disease, cardiovascular disease, neurologic complications, and malignancies. Earlier ART initiation appears to increase the probability of restoring normal CD4 counts, a normal CD4/CD8 ratio, and lower levels of immune activation and inflammation.[34-39] Individuals initiating ART very early (i.e., during the first 6 months after infection) also appear to achieve lower immune activation levels and better immune function (as assessed by vaccine responsiveness) during ART-mediated viral suppression than those who delay therapy for a few years or more.[40-42] Thus, while these questions have yet to be addressed in definitive randomized controlled trials, earlier ART initiation may result in less residual immune dysfunction during treatment, which theoretically may result in reduced risk of disease for decades to come.

Evidence Supporting the Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A number of investigations, including biological, ecological, and epidemiological studies and one randomized clinical trial, provide strong evidence that treatment of individuals with HIV can significantly reduce sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions.[43,44] Studies of HIV-serodiscordant heterosexual couples have demonstrated a relationship between level of plasma viremia and risk of HIV transmission—when plasma HIV RNA levels are lower, transmission events are less common.[1,2]

Most significantly, the multi-continental HPTN 052 trial enrolled 1,763 HIV-serodiscordant couples in which the partner with HIV was ART naive with a CD4 count of 350 to 550 cells/mm^3 at enrollment to compare the effect of immediate ART versus delayed therapy (not started until CD4 count <250 cells/mm^3) on HIV transmission to the partner who did not have HIV.[45] At study entry, 97% of the participants reported to be in a heterosexual monogamous relationship. All study participants were counseled on behavioral modification and condom use. The interim results reported 28 linked HIV transmission events during the study period, with only one event in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04; 95% CI, 0.01–0.27; $P < 0.001$). The final results of this study showed a sustained 93% reduction of HIV transmission within couples when the partner with HIV was taking ART as prescribed and viral load was suppressed.[2] Notably, there were only eight cases of HIV transmission within couples after the partner with HIV started ART; four transmissions occurred before the partner with HIV

was virologically suppressed and four other transmissions occurred during virologic failure. These results provide evidence that suppressive ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied. This study, as well as other observational studies and modeling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission.[3,46-49] HPTN 052 was conducted in heterosexual couples and not in populations at risk of HIV transmission via male-to-male sexual contact or needle sharing. In addition, in this clinical trial, adherence to ART was excellent. However, the prevention benefits of effective ART observed in HPTN 052 can reasonably be presumed to apply broadly. Therefore, the Panel recommends that ART be offered to individuals who are at risk of transmitting HIV to sexual partners **(AI)**. Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen. Clinicians should also stress that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STIs.

Prevention of Perinatal Transmission

As noted above, effective ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, use of combination ART during pregnancy has reduced the rate of perinatal transmission of HIV from approximately 20% to 30% to 0.1% to 0.5%.[50,51] ART is thus recommended for all pregnant women with HIV, for both maternal health and for prevention of HIV transmission to the newborn. In ART-naive pregnant women ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy (see Perinatal Guidelines).

Considerations When Initiating Antiretroviral Therapy

ART regimens for treatment-naive patients currently recommended in this guideline (see What to Start) can suppress and sustain viral loads below the level of quantification in most patients who adhere to their regimens. Most of the recommended regimens have low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

Optimizing Adherence and Retention in Care

The key to successful ART in maintaining viral suppression is adherence to the prescribed regimen. Treatment failure and resultant emergence of drug resistance mutations may compromise future treatment options. While optimizing adherence and linkage to care 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.[52] In both the START[8] and TEMPRANO[9] trials, participants randomized to immediate ART achieved higher rates of viral suppression than those randomized to delayed ART. Nevertheless, it is important to discuss strategies to optimize adherence and retention in care with patients before ART initiation.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, active substance abuse, unstable housing, other 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. Nevertheless, clinicians are often inaccurate in predicting ART adherence and ART reduces morbidity and mortality even in patients with relatively poor adherence and established drug resistance. Thus, mental illness, substance abuse, 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 possibly the type of ART regimen to recommend (see What to Start).

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

Since many individuals may fail to engage in care during the delay between 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 engagement in care and increase the proportion of individuals who achieve and maintain ART-mediated viral suppression. This strategy was recently tested in a randomized controlled trial of 377 individuals in South Africa who had recently received HIV diagnoses. Those randomized to receive immediate ART on the day of diagnosis were significantly more likely than those randomized to usual care (three to five additional visits with adherence counseling over 2 to 4 weeks prior to ART initiation) to be virally suppressed at 10 months (64% vs. 51%).[53] Similar improvements in both the proportion of participants retained in care achieving viral suppression and survival at the end of 1 year were recently reported in a randomized controlled trial of same-day ART initiation conducted in Haiti.[54] While there are many differences between the health care systems, structural barriers to engagement in care, and underlying HIV and TB epidemics in South Africa and Haiti that limit the generalizability of these findings to the United States, these studies suggested that same-day initiation of ART may be feasible and could potentially improve clinical outcomes. While no randomized controlled trials have been performed in the United States, a recent pilot study of 39 individuals in San Francisco suggested that initiating ART on the same day of HIV diagnosis might modestly shorten the time to achieving viral suppression.[55] It should be emphasized, however, that ART initiation on the same day of HIV diagnosis is resource-intensive, requiring "on-call" clinicians, nurses, social workers, and laboratory staff to coordinate the patient transportation, clinical evaluation, counseling, accelerated insurance coverage, required intake laboratory testing, and systems in place to assure linkage to ongoing care. As these resources may not be available in all settings and the long-term clinical benefits of same-day ART initiation have yet to be proven in the United States, this approach remains investigational.

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."[56,57] There are limited data on the role of ART in these individuals. Given the clear benefit of ART regardless of CD4 count from the START and TEMPRANO studies, delaying ART to see if a patient becomes an elite controller after initial diagnosis 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 clearly recommended for controllers with evidence of HIV disease progression, as defined by declining CD4 counts or development of HIV-related complications. Nonetheless, even elite controllers with normal CD4 counts also have evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS related diseases.[56,58-60] One observational study suggests that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[61] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[62] Whether this potential immunologic benefit of ART in elite controllers outweighs potential ART toxicity and results in clinical benefit is unclear. Unfortunately, randomized controlled trials to address this question are unlikely, 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 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. Nevertheless, there is a clear theoretical rationale for prescribing ART to HIV 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 similar to those observed in adults. Historically, 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.[63] Because youth often face multiple 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 accepting and adhering to therapy. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support (see Adolescents with HIV).[64]

Conclusion

The results of definitive randomized controlled trials support the Panel's recommendation to initiate ART to all individuals with HIV, regardless of CD4 cell count. Early diagnosis of HIV infection, followed by prompt ART initiation, has clear clinical benefits in reducing morbidity and mortality for patients with HIV and decreasing HIV transmission to their sexual partners. Although there are certain clinical and psychosocial factors that may occasionally necessitate a brief delay in ART, ART should be started as soon as possible. Clinicians should educate patients on the benefits and risks of ART and the importance of adherence.

References:

1. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921-929. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10738050.
2. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830-839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27424812.
3. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373(9657):48-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19038438.
4. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. *Clin Infect Dis*. 2010;50(11):1512-1520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20415573.
5. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17205456.
6. Palella FJJ, Armon C, Chmiel JS, et al. CD4 cell count at initiation of ART, long-term likelihood of achieving CD4 >750 cells/mm3 and mortality risk. *The Journal of antimicrobial chemotherapy*. 2016;71(9):2654-2662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27330061.
7. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PloS one*. 2013;8(12):e81355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24367482.
8. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26192873.
9. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26193126.
10. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2016. Available at: https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0.

11. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2017. Available at: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0.

12. Gopal S, Patel MR, Achenbach CJ, et al. Lymphoma immune reconstitution inflammatory syndrome in the center for AIDS research network of integrated clinical systems cohort. *Clin Infect Dis*. 2014;59(2):279-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24755860.

13. Gopal S, Patel MR, Yanik EL, et al. Association of early HIV viremia with mortality after HIV-associated lymphoma. *AIDS*. 2013;27(15):2365-2373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23736149.

14. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. 2011;52(11):1374-1383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21596680.

15. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370(26):2487-2498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24963568.

16. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. 2005;41(10):1483-1497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16231262.

17. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *Journal of acquired immune deficiency syndromes*. 2009;51(2):130-134. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19365271.

18. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PloS one*. 2009;4(5):e5575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19440326.

19. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *Journal of acquired immune deficiency syndromes*. 2009;50(2):148-152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19131895.

20. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20181971.

21. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365(16):1492-1501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22010915.

22. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22010913.

23. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22010914.

24. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16988643.

25. Wolbers M, Bucher HC, Furrer H, et al. Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. *HIV Med*. 2008;9(6):397-405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18410354.

26. Centers for Disease Control and Prevention (CDC). Late HIV testing - 34 states, 1996-2005. *MMWR Morbidity and mortality weekly report*. 2009;58(24):661-665. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19553901.

27. Grigoryan A, Hall HI, Durant T, Wei X. Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996-2004. *PloS one*. 2009;4(2):e4445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19214229.

28. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19339714.

29. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009;373(9672):1352-1363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19361855.

30. CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1

seroconverters. *Arch Intern Med*. 2011;171(17):1560-1569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21949165.

31. Cain LE, Logan R, Robins JM, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Ann Intern Med*. 2011;154(8):509-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21502648.
32. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med*. 1997;337(11):725-733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9287227.
33. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363(3):257-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20647201.
34. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23323898.
35. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis*. 2003;187(10):1534-1543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12721933.
36. Mocroft A, Phillips AN, Gatell J, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet*. 2007;370(9585):407-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17659333.
37. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis*. 2009;48(6):787-794. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19193107.
38. Lange CG, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *AIDS*. 2003;17(14):2015-2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14502004.
39. Robbins GK, Spritzler JG, Chan ES, et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group protocol 384. *Clin Infect Dis*. 2009;48(3):350-361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19123865.
40. Jain V, Hartogensis W, Bacchetti P, et al. Antiretroviral therapy initiated within 6 months of HIV infection is associated with lower T-cell activation and smaller HIV reservoir size. *J Infect Dis*. 2013;208(8):1202-1211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23852127.
41. Burdo TH, Lentz MR, Autissier P, et al. Soluble CD163 made by monocyte/macrophages is a novel marker of HIV activity in early and chronic infection prior to and after anti-retroviral therapy. *J Infect Dis*. 2011;204(1):154-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21628670.
42. Okulicz JF, Le TD, Agan BK, et al. Influence of the timing of antiretroviral therapy on the potential for normalization of immune status in human immunodeficiency virus 1-infected individuals. *JAMA internal medicine*. 2015;175(1):88-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25419650.
43. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS*. 2000;14(2):117-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10708281.
44. Coombs RW, Reichelderfer PS, Landay AL. Recent observations on HIV type-1 infection in the genital tract of men and women. *AIDS*. 2003;17(4):455-480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12598766.
45. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21767103.
46. Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *Journal of acquired immune deficiency syndromes*. 2005;40(1):96-101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16123689.
47. Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS*. 2006;20(1):85-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16327323.
48. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet*. 2008;372(9635):314-320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18657710.

49. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011;25(4):473-477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21160416.

50. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.

51. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18453857.

52. Uy J, Armon C, Buchacz K, Wood K, Brooks JT. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *Journal of acquired immune deficiency syndromes*. 2009;51(4):450-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19474757.

53. Rosen S, Maskew M, Fox MP, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: The RapIT randomized controlled trial. *PLoS medicine*. 2016;13(5):e1002015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27163694.

54. Koenig SP, Dorvil N, Devieux JG, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial. *PLoS medicine*. 2017;14(7):e1002357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28742880.

55. Pilcher CD, Ospina-Norvell C, Dasgupta A, et al. The effect of same-day observed initiation of antiretroviral therapy on HIV viral load and treatment outcomes in a US public health setting. *Journal of acquired immune deficiency syndromes*. 2017;74(1):44-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27434707.

56. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis*. 2008;197(1):126-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18171295.

57. Choudhary SK, Vrisekoop N, Jansen CA, et al. Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease. *J Virol*. 2007;81(16):8838-8842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17537849.

58. Pereyra F, Lo J, Triant VA, et al. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS*. 2012;26(18):2409-2412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23032411.

59. Hsue PY, Hunt PW, Schnell A, et al. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS*. 2009;23(9):1059-1067. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19390417.

60. Krishnan S, Wilson EM, Sheikh V, et al. Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J Infect Dis*. 2014;209(6):931-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24185941.

61. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection. *J Infect Dis*. 2015;211(11):1692-1702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25512624.

62. Hatano H, Yukl SA, Ferre AL, et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. *PLoS pathogens*. 2013;9(10):e1003691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24130489.

63. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *Journal of acquired immune deficiency syndromes*. 2011;58(2):193-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21826014.

64. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS patient care and STDs*. 2009;23(3):185-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19866536.

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) 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 (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir).
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as Recommended Initial Regimens for Most People with HIV (in alphabetical order):
  - Dolutegravir/abacavir/lamivudine[a]—**only** for patients who are HLA-B*5701-negative **(AI)**
  - Dolutegravir plus tenofovir/emtricitabine[a,b] **(AI)**
  - Elvitegravir/cobicistat/tenofovir/emtricitabine[b] **(AI)**
  - Raltegravir plus tenofovir/emtricitabine[a,b] (**AI** for tenofovir disoproxil fumarate, **AII** for tenofovir alafenamide)[a,b]
- To address individual patient characteristics and needs, the Panel also provides a list of Recommended Initial Regimens in Certain Clinical Situations (Table 6).
- 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 testing results, comorbid conditions, access, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 8 highlights the advantages and disadvantages of different components in a regimen.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

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] Lamivudine may substitute for emtricitabine or vice versa.

[b] Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two forms of tenofovir approved by the 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 25 antiretroviral (ARV) drugs in six mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). In addition, two drugs, ritonavir (RTV or r) and cobicistat (COBI or c) are used solely as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of some ARV drugs (e.g., PIs and the INSTI elvitegravir [EVG]).

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide (TAF)/emtricitabine (FTC) or tenofovir disoproxil fumarate (TDF)/FTC, plus a drug from one of three drug classes: an INSTI, an NNRTI, or a PK-enhanced 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 T lymphocyte (CD4) cell increases in most persons with HIV.[1-3]

Supporting Evidence and Rationale Used for Panel's Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In select cases, the Panel considers data from abstracts presented at major scientific meetings. The Panel considers published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates 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 or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (especially rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include medications approved by the FDA based on bioequivalence or relative bioavailability studies demonstrating 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 new medication replaces an existing medication from the same class in patients who have achieved virologic suppression on an initial regimen. 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 from trials conducted in treatment-naive patients and bioequivalence/bioavailability studies. 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, post-marketing safety data, observational cohort data published in peer-reviewed publications, and the experience of clinicians and community members who are actively engaged in patient care.

The Panel reviewed the available data to arrive at two regimen classifications for ARV-naive patients: (1) Recommended Initial Regimens for Most People with HIV and (2) Recommended Initial Regimens in Certain Clinical Situations (Table 6). 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. Examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous are outlined in Table 7.

There are many other ARV regimens that are effective for initial therapy, but have disadvantages 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 other regimens are no longer included in Table 6. A person with HIV who is virologically suppressed and who is not experiencing any adverse effects on a regimen that is not listed in Table 6 need not necessarily change to a regimen that is in that table.

Regimens and medications listed in Table 9 are not recommended. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 9 to a recommended regimen.

In addition to these tables, a number of tables presented below and at the end of the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (Adult and Adolescent Guidelines) provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 8 lists the potential advantages and disadvantages of the different antiretroviral drug components. Appendix B, Tables 1–6 lists characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 7 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 the Adult and Adolescent Guidelines, there have been several important changes in the Panel's recommendations for initial therapy of people with HIV. Among these changes, the following deserve emphasis:

- INSTI-based regimens are recommended as initial therapy for most people with HIV. In large clinical trials and in clinical practice, INSTI-based regimens have achieved high rates of virologic suppression and often have greater tolerability than PI- or NNRTI-based regimens.
- In certain clinical situations, a PI- or an NNRTI-based regimen may be preferred. In recognition of these situations, a new category—called Recommended Initial Regimens in Certain Clinical Situations—has been added to the Guidelines.
- Darunavir (DRV)-based regimens have been moved to the category of Recommended Initial Regimens in Certain Clinical Situations based on trials showing improved outcomes with INSTI-based regimens when compared with ritonavir-boosted darunavir (DRV/r), in part because of greater tolerability of the former. An example of a situation in which a DRV-based regimen may still be preferred is when a high genetic barrier to resistance is particularly important, such as when there is substantial concern regarding a person's adherence or when antiretroviral therapy (ART) should be initiated before resistance test results are available. Other examples of important clinical considerations that may favor specific regimens are included in Table 7.
- Recommended NRTI combinations continue to be ABC/3TC and one of the tenofovir products—TAF or TDF—with FTC. With additional data since the last revision, the relative advantages of the two available tenofovir formulations have become clearer. TAF has less bone and kidney toxicity than TDF and is therefore particularly advantageous in people with underlying bone and kidney disease or those at high risk for these conditions. TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. Safety, cost, and access are among the factors to consider in choosing between these two formulations of tenofovir. Guidance for the clinician on choosing between ABC-, TAF-, and TDF-containing regimens are featured in these guidelines.

Table 6. Recommended Antiretroviral Regimens for Initial Therapy

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, access, and resistance test results. Drug classes and regimens within each class are arranged first by evidence rating, and, when ratings are equal, in alphabetical order. **Table 7 provides 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.
INSTI + 2 NRTIs: • DTG/ABC/3TC[a] **(AI)**—if HLA-B*5701 negative • DTG + tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC) • EVG/c/tenofovir[b]/FTC (**AI** for both TAF/FTC and TDF/FTC) • RAL[c] + tenofovir[b]/FTC[a] (**AI** for TDF/FTC, **AII** for TAF/FTC)
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 less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).
Boosted PI + 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV) • (DRV/c or DRV/r) + tenofovir[b]/FTC[a] (**AI** for DRV/r and AII for DRV/c) • (ATV/c or ATV/r) + tenofovir[b]/FTC[a] **(BI)** • (DRV/c or DRV/r) + ABC/3TC[a] **—if HLA-B*5701–negative (BII)** • (ATV/c or ATV/r) + ABC/3TC[a] **—if HLA-B*5701–negative and HIV RNA <100,000 copies/mL** (**CI** for ATV/r and **CIII** for ATV/c) NNRTI + 2 NRTIs: • EFV + tenofovir[b]/FTC[a] (**BI** for EFV/TDF/FTC and **BII** for EFV + TAF/FTC) • RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** INSTI + 2 NRTIs: • RAL[c] + ABC/3TC[a] **(CII)—if HLA-B*5701–negative and HIV RNA < 100,000 copies/mL** Regimens to Consider when ABC, TAF, and TDF Cannot be Used:[d] • DRV/r + RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** • LPV/r + 3TC[a] (BID)[e] **(CI)**

[a] 3TC may be substituted for FTC, or vice versa, if a non–fixed-dose NRTI combination is desired.

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

[c] RAL can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily.

[d] Several other NRTI-limiting treatment strategies are under investigation. See the section titled Selected Strategies That Are Under Evaluation and Not Yet Recommended below for discussion regarding these regimens.

[e] LPV/r plus 3TC is the only boosted PI plus 3TC regimen with published 48-week data in a randomized controlled trial in ART-naive patients. Limitations of LPV/r plus 3TC include twice-daily dosing, high pill burden, and greater rates of gastrointestinal side effects than other PIs.

Note: The following are available as coformulated drugs: ABC/3TC, ATV/c, DRV/c, DTG/ABC/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, LPV/r, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, and TDF/FTC.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BID = twice daily; CD4 = CD4 T lymphocyte; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Selecting an Initial Antiretroviral Regimen

Initial therapy generally consists of two NRTIs combined with an INSTI, an NNRTI, or a PK-enhanced PI.

Choosing the Two Nucleoside Reverse Transcriptase Inhibitors

All the Recommended Initial Regimens for Most People with HIV and most of the Recommended Initial Regimens in Certain Clinical Situations include an NRTI combination of ABC/3TC, TAF/FTC, or TDF/FTC, each of which is available as a fixed-dose combination tablet. The choice of NRTI combination is usually guided by differences between ABC, TAF, and TDF, because FTC and 3TC have few adverse events and comparable efficacy. The main advantages of TAF and TDF over ABC are their activity against hepatitis B virus (HBV) and the fact that HLA-B*5701 testing is not required for their use. Moreover, TDF has been associated with lower lipid levels than TAF and ABC. However, TDF use has been associated with declines in kidney function, proximal renal tubulopathy (leading to proteinuria and phosphate wasting), and reductions in bone mineral density (BMD). These tenofovir toxicities are less common with TAF, which results in lower plasma tenofovir concentrations than TDF. As a result, the main advantages of TAF over TDF are TAF's more favorable effects on renal markers and BMD.[4-6] The main advantages of ABC over TDF are that it does not require dose adjustment in patients with renal insufficiency and has less nephrotoxicity and less deleterious effects on BMD than TDF. However, ABC use has been linked to cardiovascular events in some, but not all, observational studies. Considerations germane to the choice between TAF, TDF, and ABC in specific clinical scenarios are summarized in Table 7, Table 8, and in the section on dual-NRTI options below. For patients in whom ABC, TAF, or TDF cannot be used, recommendations for NRTI-limiting treatment regimens are given in Table 6 and in the section below on Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used.

Choosing Between an INSTI-, PI-, or NNRTI-Based Regimen

The choice between an INSTI, PI, or NNRTI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, genetic barrier to resistance, adverse effects profile, and convenience. The patient's comorbidities, concomitant medications, and the potential for drug-drug interactions should also be considered (see Tables 7 and 8 for guidance). The Panel's Recommended Initial Regimens for Most People with HIV as listed in Table 6 include an INSTI plus two NRTIs. For most patients, an INSTI-containing regimen will be highly effective, have few adverse effects, and (with raltegravir [RAL] and dolutegravir [DTG]) have no significant CYP3A4-associated drug interactions. In addition, in several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI was better tolerated with fewer treatment discontinuations.[7-9] For these reasons, all three currently available INSTIs are included among the Recommended Initial Regimens for Most People with HIV. An exception is in those individuals with uncertain adherence or in whom treatment needs to begin before resistance testing results are available (e.g., during acute HIV infection, pregnancy, and in the setting of certain opportunistic infections). In this context, DRV/r may have an important role given the low rate of transmitted PI resistance, its high genetic barrier to resistance, and low rate of treatment-emergent resistance during many years of clinical experience. DTG may also be considered for patients who must start ART before resistance testing results are available. Because of its high barrier to resistance, DTG resistance is uncommon in patients experiencing virologic failure while on a DTG-containing initial regimen, and transmitted resistance has not yet been identified. Ritonavir-boosted atazanavir (ATV/r) has demonstrated excellent virologic efficacy in clinical trials and has relatively few metabolic adverse effects in comparison to other boosted-PI regimens; however, a randomized clinical trial showed that ATV/r had a higher rate of adverse effect-associated drug discontinuation than DRV/r and RAL.[7] In a substudy of this same trial, and in a separate cross-sectional cohort study, ATV/r use was associated with less progression of atherosclerosis as measured by carotid artery intima medial thickness.[10,11] Whether this finding will translate into a clinical benefit is uncertain. Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir [FPV], indinavir [IDV], and ritonavir-boosted lopinavir [LPV/r]) and an increased risk of cardiovascular events, while this association was not seen with ATV.[12-15] Another

observational cohort of predominantly male participants showed a lower rate of cardiovascular events in participants receiving ATV-containing regimens compared with other regimens.[16] Further study is needed.

NNRTI-based (efavirenz [EFV] or rilpivirine [RPV]) regimens may be optimal choices for some patients, although these drugs have low genetic barriers to resistance. EFV has a long track record of widespread use in the United States and globally, and its minimal PK interaction with rifamycins makes it an attractive option for patients who require concomitant treatment for tuberculosis (TB). Most EFV-based regimens have excellent virologic efficacy, 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 makes EFV-based regimens less tolerable than other regimens. RPV has fewer adverse effects than EFV, is available as one of the smallest coformulated single tablets, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with high baseline HIV RNA (>100,000 copies/mL) and low CD4 count (<200 cells/mm^3).

Factors to Consider When Selecting an Initial Regimen

When selecting a regimen for an individual person with HIV, a number of patient- and regimen-specific characteristics should be considered. The goal is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen for the patient in order to achieve sustained virologic control. Some of the factors can be grouped into the following categories:

Initial Characteristics to Consider in All Persons with HIV:

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 count
- HIV genotypic drug resistance testing results (based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase [RT] and protease [PR] genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs).
- HLA-B*5701 status
- Individual preferences
- Anticipated adherence to the regimen

Specific Comorbidities or Other Conditions:

- Cardiovascular disease, hyperlipidemia, renal disease, liver disease, osteopenia/osteoporosis or conditions associated with BMD loss, psychiatric illness, neurologic disease, drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or pregnancy potential. Clinicians should refer to the latest Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States (Perinatal Guidelines) for more detailed recommendations on the safety and effectiveness of ARV drugs during pregnancy.
- Coinfections: HBV, hepatitis C virus (HCV), TB

Regimen-Specific Considerations:

- Regimen's genetic barrier to resistance
- Potential adverse effects
- Known or potential drug interactions with other medications (see Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of fixed-dose combination formulations, food requirements)
- Cost (see Cost Considerations and Antiretroviral Therapy)

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios
(page 1 of 4)

This table is designed to guide clinicians in choosing an initial 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 initial choice of 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 8 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 + RAL	A higher rate of virologic failure has been observed in those with low pretreatment CD4 count.
	HIV RNA >100,000 copies/mL	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r + RAL	Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA.
	HLA-B*5701–positive	**Do not use ABC-containing regimens.**	Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele.
	ARV must be started before HIV drug resistance results are available (e.g., in a person with acute HIV or when a rapid initiation of ART is warranted). See Initiation of Antiretroviral Therapy.	**Avoid NNRTI-based regimens.** Recommended ART Regimens: • (DRV/r or DRV/c) + tenofovir[a]/FTC; *or* • DTG + tenofovir[a]/FTC	Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance. Resistance to DRV and DTG emerges slowly; transmitted resistance to DRV is rare and transmitted resistance to DTG has not been reported to date.
ART-Specific Characteristics	A one-pill, once-daily regimen is desired.	STR Options Include: • DTG/ABC/3TC • EFV/TDF/FTC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use RPV-based regimens if HIV RNA >100,000 copies/mL and CD4 count <200/mm^3. Since RPV-containing STRs are smaller in size than other STRs, they may be considered when a person has difficulty swallowing a larger pill. Do not use DTG/ABC/3TC if patient is HLA-B*5701–positive. See Appendix B, Table 7 for recommendations on ARV dose modification in the setting of renal impairment.
	Food effects	Regimens that Can be Taken Without Regard to Food: • RAL- or DTG-based regimens	Oral bioavailability of these regimens is not significantly affected by food.

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios
(page 2 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics, continued	Food effects, continued	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 at least 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)	**Avoid TDF.** Use ABC or TAF. ABC may be used if HLA-B*5701–negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC + (EFV or ATV/r). TAF may be used if CrCl >30 mL/min. Consider avoiding ATV. Other Options When ABC or TAF Cannot be Used: • LPV/r + 3TC; *or* • RAL + DRV/r (if CD4 count >200 cells/mm^3, HIV RNA <100,000 copies/mL) • See text for discussion of alternative NRTI-limiting regimens.	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction reported in patients using TDF in conjunction with RTV-containing regimens. 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. See Appendix B, Table 7 for recommendations on ARV dose modification in patients with renal insufficiency.
	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 7 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	Osteoporosis	**Avoid TDF.** Use ABC or TAF. ABC may be used if HLA-B*5701–negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC + (EFV or ATV/r).	TDF is associated with decreases in bone mineral density along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF and ABC are associated with smaller declines in bone mineral density than TDF.
	Psychiatric illnesses	**Consider avoiding EFV- and RPV-based regimens.** Patients on INSTI-based regimens with pre-existing 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 as Initial Therapy based on Specific Clinical Scenarios
(page 3 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	HIV-associated dementia (HAD)	**Avoid EFV-based regimens if possible.** Favor DTG- or DRV-based regimens.	EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on improvement of HAD-related symptoms. There is a theoretical CNS penetration advantage of DTG- or DRV-based regimens.
	Narcotic replacement therapy required	**If patient is receiving methadone, consider avoiding EFV-based regimens.** If EFV is used, an increase in methadone dose may be necessary.	EFV reduces methadone concentrations and may lead to withdrawal symptoms.
	High cardiac risk	DTG-, RAL- or RPV-based regimens may be advantageous in this setting. Consider avoiding ABC- and LPV/r -based regimens. If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen.	An increased CV risk has been observed in some studies. Observational cohort studies reported an association between some PIs (DRV, IDV, FPV, and LPV/r) and an increased risk of CV events, while this has not been seen with ATV (see text); further study is needed.
	Cardiac QTc interval prolongation	Consider avoiding EFV- or RPV-based regimens if 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.
	Hyperlipidemia	The Following ARV Drugs Have Been Associated with Dyslipidemia: • PI/r or PI/c • EFV • EVG/c	DTG, RAL, and RPV have fewer lipid effects. TDF has been associated with lower lipid levels than ABC or TAF.
	Patients with history of poor adherence to ARV or inconsistent engagement in care	Consider boosted PI- or DTG-based regimens.	These regimens have a high genetic barrier to resistance.
	Pregnancy	Refer to the Perinatal Guidelines for specific regimen recommendations.	
Presence of Coinfections	HBV infection	Use TDF or TAF, with FTC or 3TC, whenever possible. If TDF and TAF Are Contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/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 active against HBV.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	

Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 4 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Coinfections, continued	Treating TB disease with rifamycins	TAF is **not recommended** with any rifamycin-containing regimen. If Rifampin is Used: • EFV can be used without dosage adjustment. • If RAL is used, increase RAL dose to 800 mg BID. • Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label). If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen.	• Rifamycins may significantly reduce TAF exposure. • Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PIs, INSTIs, and RPV. • Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs. • Rifabutin is a less potent inducer and is an option for patients receiving non-EFV-based regimens. Refer to Tables 18a, b, d and e for dosing recommendations for rifamycins used with different ARV agents.

[a] TAF and TDF are two approved forms of tenofovir. TAF has less 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 to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BID = twice daily; c = cobicistat; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV or r = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase

Choosing Among Different Drugs from an Antiretroviral Drug Class

The sections below provide clinicians with comparisons of different, currently recommended ARV drugs within a drug class. These comparisons include information related to the safety and virologic efficacy of different drugs based on clinical trial results and/or post-marketing data, specific factors to consider, and the rationales for the Panel's recommendations.

Dual-Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Combination Therapy

Summary

ABC/3TC, TAF/FTC, and TDF/FTC are NRTI combinations recommended for use as components of initial therapy. 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. TAF and TDF are two approved forms of tenofovir. TAF has less 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.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, either with the same[17-19] or a different (third) ARV drug (also see the discussion in the dolutegravir section).[20]

- The ACTG 5202 study, a randomized controlled trial in more than 1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each was used in combination with either EFV or ATV/r.
  - Treatment randomization was stratified on the basis of a screening HIV RNA level <100,000 copies/mL or ≥100,000 copies/mL. HLA-B*5701 testing was not required before study entry.
  - A Data Safety Monitoring Board recommended early termination of the ≥100,000 copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the ABC/3TC arm than in the TDF/FTC arm.[17] This difference in time to virologic failure between the arms was observed regardless of whether the third active drug was EFV or ATV/r.
  - There was no difference in time to virologic failure between ABC/3TC and TDF/FTC for participants who had plasma HIV RNA <100,000 copies/mL at screening.[21]
- 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 than among TDF/FTC-treated participants.[18]
- In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. Virologic efficacy was similar in the two study arms. In a subgroup analysis of patients with baseline HIV RNA ≥100,000 copies/mL, the proportion of participants who achieved HIV RNA <50 copies/mL at 96 weeks did not differ between the two regimens.[19]

Tenofovir Alafenamide Compared with Tenofovir Disoproxil Fumarate

- Two randomized double-blind phase 3 clinical trials compared the safety and efficacy of EVG/c/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min.
  - At 48 weeks, 92% of participants randomized to receive TAF and 90% of those randomized to receive TDF achieved plasma HIV RNA <50 copies/mL, demonstrating that TAF was noninferior to TDF when combined with EVG/c/FTC. Both regimens were well-tolerated. The studies did not have adequate power to assess whether renal failure and fracture rates were different between the TAF and TDF groups.[4] At 144 weeks, TAF/FTC was superior to TDF/FTC (84.2% vs. 80% of participants achieved plasma HIV RNA <50 copies/mL, respectively), largely driven by a higher rate of treatment discontinuation in the TDF arm.[22]
  - Participants in the TAF arm had significantly smaller reductions in BMD at the spine and the hip than those in the TDF arm through 144 weeks.[22]
  - Through 96 weeks, change from baseline eGFR and renal biomarkers favored EVG/c/TAF/FTC, and renal tubular function was less affected by the EVG/c/TAF/FTC regimen than by the EVG/c/TDF/FTC regimen. Clinically significant renal events, including discontinuations for renal adverse events, were less frequent in participants receiving EVG/c/TAF/FTC than in those treated with EVG/c/TDF/FTC.[23] A subset analysis of patients at high risk for chronic kidney disease showed a lower rate of at least 25% decline in eGFR in patients on EVG/c/TAF/FTC, compared to patients on EVG/c/TDF/FTC (11.5% vs. 24.9%, $P < 0.001$).[6]
  - Fasting lipid levels, including low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, increased more in the TAF group than in the TDF group at 96

weeks, with no change in total cholesterol to HDL ratio.[24]

- A phase 2 study of coformulated cobicistat-boosted DRV (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% vs. 74%) in treatment-naive patients.[25] Less proteinuria and less change in BMD were observed in the TAF arm.

- Combination TAF/FTC was also approved based on efficacy and safety data from one switch study in virologically suppressed patients.[5] This study included 663 patients with HIV RNA <50 copies/mL for at least 6 months on a regimen containing TDF/FTC. Participants were randomized to continue TDF/FTC or switch to TAF/FTC.
  - At 48 weeks, TAF/FTC was noninferior to TDF/FTC in that viral suppression was maintained by 94.3% and 93% of the participants, respectively.
  - Improvement in eGFR and renal biomarkers was more frequent in those switched to TAF/FTC. BMD improved in those switched to TAF/FTC but declined in those continuing on TDF/FTC.
  - Fasting lipid levels increased more in those who switched to TAF/FTC than in those who continued TDF/FTC.
- To assess the ability of TAF to maintain HIV and 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.[26] In this study, 96% of participants were on a TDF/FTC-containing regimen prior to the switch.
  - Those who switched to EVG/c/TAF/FTC maintained HIV suppression: 94.4% and 91.7% of participants at 24 and 48 weeks, respectively. At 24 and 48 weeks, 86.1% and 91.7% of participants had HBV DNA <29 $\log_{10}$ IU/mL.
  - Decreases in markers of proximal tubular proteinuria and biomarkers of bone turnover were seen in those who switched to EVG/c/TAF/FTC.[26]

Dual-Nucleoside Reverse Transcriptase Inhibitor Choices (In alphabetical order)

Abacavir/Lamivudine (ABC/3TC)

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in ART-naive patients.[20,27-29]

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 will have an ABC-related HSR if given this drug.[30,31] HLA-B*5701 testing should precede use of ABC. ABC should not be given to patients who test positive for HLA-B*5701 and, based on a positive test result, ABC hypersensitivity should be noted on a 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 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 MI, particularly in participants with pre-existing cardiac risk factors.[13,32]

- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and

cardiovascular events. Some studies have found an association.[33-40] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[12,41-44]

- 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 single-tablet regimen 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 dosage adjustment is required in patients with renal dysfunction.

The Panel's Recommendations:

- ABC should only be prescribed 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 fixed-dose combination, the Panel classifies DTG/ABC/3TC as a Recommended Initial Regimen for Most People with HIV **(AI)** (see discussion of DTG in this section regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, ATV/c, DRV/c, DRV/r, or RAL is only recommended for patients with pretreatment HIV RNA <100,000 copies/mL. See Table 6 for more detailed recommendations on use of ABC/3TC with these drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

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 (described below).

Lipid Effects:

- In the randomized controlled trials in ART-naive patients, as well as in switch studies (described below), 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 TDF. The clinical significance of this finding is not clear.[4-6]

Other Factors and Considerations:

- TAF/FTC is available in fixed-dose drug combinations with EVG/c or RPV, allowing the regimens to be administered as a single pill taken once daily with food.

- TAF-containing compounds 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 (see Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV on Antiretroviral Therapy).
- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair of the ART regimen because the drugs have activity against both viruses (see HBV/HIV Coinfection).[26]

The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[45] and its availability as a component of various fixed-dose combinations, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most persons with HIV when prescribed with DTG **(AI)**, EVG/c **(AI)**, and RAL **(AII)**.

Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)

TDF, with either 3TC or FTC, has been studied in combination with EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.[46,47-55]

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.[56,57] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females)[58] and pre-existing renal impairment.[59] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested a greater risk of renal dysfunction 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.[57,59-63]

Bone Effects:

- While 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 comparing TDF/FTC with ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.[64,65] BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF (see above).
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.[66]

Other Factors and Considerations:

- TDF/FTC is available in fixed-dose drug combinations with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill, taken once daily.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy). In patients who have pre-existing renal insufficiency (creatinine clearance [CrCl] <60 mL/min),[67] use of TDF should generally be avoided. If TDF is used, dosage adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 7 for dosage recommendations).
- Both TDF and FTC are active against HBV. In patients with HIV/HBV coinfection, TDF/FTC may be used as the NRTI pair of the ART regimen because the drugs have activity against both viruses (also see HBV/HIV Coinfection section).

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 fixed dose formation drugs, the Panel considers TDF/FTC a Recommended NRTI combination for initial ART in most persons with HIV when combined with DTG, EVG/c, 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.

Integrase Strand Transfer Inhibitor–Based Regimens

Summary

Three INSTIs—DTG, EVG, and RAL—are currently approved for ARV-naive patients with HIV. DTG and EVG are currently available as components of one-tablet, once-daily complete regimens: DTG is coformulated with ABC/3TC; EVG is coformulated with a PK enhancer (COBI) and TAF/FTC or TDF/FTC. All INSTIs are generally well tolerated, though there are reports of insomnia in some patients. Depression and suicidal ideation, primarily in patients with a history of psychiatric illnesses, have rarely been reported in patients receiving INSTI-based regimens. INSTI-based regimens are Recommended Initial Regimens for Most People with HIV.

Integrase Strand Transfer Inhibitor-Based Regimens (In alphabetical order)

Dolutegravir (DTG)

DTG is an INSTI with a higher genetic barrier to resistance than EVG or RAL. In treatment-naive patients, DTG is given once daily, with or without food.

Efficacy in Clinical Trials:

The efficacy of DTG in treatment-naive patients has been evaluated in several fully powered randomized controlled clinical trials. In these three 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.

- 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 regimen, either ABC/3TC or TDF/FTC, to 822 participants. At week 96, DTG was noninferior to RAL.[55]
    - The SINGLE trial compared DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At week 48, DTG was superior to EFV, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.[20] At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[68]
- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to DRV/r 800/100 mg once daily, each in combination with investigator-selected ABC/3TC or TDF/FTC. At week 48, DTG was superior to DRV/r because of the higher rate of discontinuation in the DRV/r arm.[69,70] The difference in response rates favoring DTG was greater in patients with pretreatment HIV RNA levels >100,000 copies/mL. At week 96, DTG remained superior to DRV/r.[71]
- The ARIA trial is an open-label, phase 3b randomized controlled trial, comparing the efficacy and safety of DTG/ABC/3TC to ATV/r plus TDF/FTC in ART-naive, nonpregnant women. At week 48, 82% of participants in the DTG group achieved HIV RNA viral loads <50 copies/mL compared with 71% in the ATV group ($P = 0.005$). The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.[72]

Adverse Effects:

- DTG is generally well tolerated. The most common adverse reactions of moderate to severe intensity with an incidence ≥2% in the clinical trials were insomnia and headache. Cases of HSRs were reported in <1% of trial participants.
- Case series of neuropsychiatric adverse events (sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported.[73,74] Two observational cohort studies reported a higher frequency of neuropsychiatric adverse events leading to treatment discontinuation in patients receiving DTG than in patients receiving other INSTIs.[75,76] However, analyses of data from large randomized controlled trials as well as a health care database demonstrated similar rates of neuropsychiatric adverse events with DTG-based regimens versus other ARV regimens,[77] with neuropsychiatric events rarely leading to DTG discontinuation. Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs,[78] and not only DTG. Further studies will be needed to precisely clarify the true incidence and implications of these neuropsychiatric events. A pathophysiologic mechanism for these neuropsychiatric adverse events has not been defined.

Other Factors and Considerations:

- DTG decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment (mean increase in serum creatinine was 0.11 mg/dL after 48 weeks).
- DTG has fewer drug interactions than EVG/c. See Drug Interactions for specific drug-drug interactions which require dosage adjustment.
- DTG absorption may be reduced when the ARV is coadministered with polyvalent cations (see Drug Interactions). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have not been reported in patients receiving DTG as part of a three-drug regimen for initial therapy, which suggests that DTG has a higher genetic barrier to resistance than other INSTIs.

The Panel's Recommendation:

- On the basis of clinical trial data, the Panel categorizes DTG in combination with ABC/3TC **(AI)**, TAF/FTC **(AI)**, or TDF/FTC **(AI)** as a Recommended Initial Regimen for Most People with HIV.

Elvitegravir (EVG)

EVG is available as a component of two single-tablet regimens: 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 for once-daily dosing of the combination.

Efficacy in Clinical Trials:

- The efficacy of EVG/c/TDF/FTC in ARV-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.[79]
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.[80]
  - In a randomized, blinded trial performed in women with HIV, EVG/c/TDF/FTC had superior efficacy when compared to ATV/r plus TDF/FTC, in part because of a lower rate of treatment discontinuation.[9]

- The efficacy of EVG/c/TAF/FTC in ARV-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with eGFR ≥50 mL/min.[4,24]
  - At 48 and 96 weeks, TAF was noninferior to TDF when both were combined with EVG/c/FTC, whereas EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC at 144 weeks.[22]

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[79,80]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[81]
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see discussion under DTG).

Other Factors and Considerations:

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI inhibits CYP3A, it interacts with a number of medications that are metabolized by this enzyme (see Drug Interactions).[82]
- EVG plasma concentrations are lower when it is administered simultaneously with polyvalent cation-containing antacids or supplements (see Drug Interactions). Separate EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacid administration by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG dosing.
- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.[83] Patients with a confirmed increase in serum creatinine greater than 0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be closely monitored and evaluated for evidence of TDF-related proximal renal tubulopathy.[63]
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl <70 mL/min.[63]
- EVG/c/TAF/FTC **is not recommended** for patients with pretreatment estimated CrCl <30 mL/min.
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.[79,80] These mutations conferred cross-resistance to RAL, with most retaining susceptibility to DTG.

The Panel's Recommendation:

- On the basis of the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as Recommended Initial Regimens for Most People with HIV (AI). EVG/c/TAF/FTC should only be used in people with estimated CrCl ≥30 mL/min; EVG/c/TDF/FTC should only be used 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 in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.[51] RAL was superior to EFV at 4 and 5 years,[54,84]

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 in combination with investigator-selected ABC/3TC or TDF/FTC. At week 96, DTG was noninferior to RAL.
- The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 and 125 participants with baseline viral loads ≥100,000 copies/mL and <100,000 copies/mL, respectively) received RAL in combination with ABC/3TC. After 96 weeks, there was no difference in virologic response between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.[55]
- ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens containing 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 ritonavir-boosted protease inhibitor (PI/r) arms than in the RAL arm, and BMD decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.[7]

RAL 1200 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 1200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each 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.[85]

Adverse Effects:

- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.[86]
- Neuropsychiatric adverse events (for example, insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see discussion under DTG).[77,87]

Other Factors and Considerations:

- RAL can be administered as 1200 mg (two 600-mg tablets) once a day or as 400 mg twice daily with or without food in ART-naive patients.
- Coadministration of RAL as either 400 mg twice daily or 1200 mg once daily with aluminum- 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 1200 mg once daily. Polyvalent cation-containing supplements may also reduce absorption of RAL. See Table 18d for dosing recommendations.
- RAL has a lower genetic barrier to resistance than RTV-boosted PIs and DTG.

The Panel's Recommendations:

- On the basis of these clinical trial data, the Panel considers RAL given as 1200 mg (two 600-mg tablets) once daily or as 400 mg twice daily plus TDF/FTC **(AI)** or TAF/FTC **(AII)** as a Recommended Initial Regimen for Most People with HIV.
- Because fewer patients have received RAL plus ABC/3TC in clinical trials or practice and there has not been a randomized trial comparing ABC/3TC plus RAL to TDF/FTC plus RAL, the Panel categorizes RAL plus ABC/3TC as a Recommended Initial Regimen in Certain Clinical Situations **(BII)**.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Summary

Five NNRTIs (delavirdine [DLV], EFV, etravirine [ETR], nevirapine [NVP], and RPV) are currently FDA-approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs are the prevalence of NNRTI-resistant viral strains in ART-naive patients[88] and the drugs' low genetic barrier for the development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients (see Drug-Resistance Testing). High-level resistance to all NNRTIs (except ETR) may occur with a single mutation; within-class cross-resistance is common. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.[89,90] EFV- and RPV-based regimens are now categorized as Recommended Initial Regimens in Certain Clinical Situations for ART-naive patients for the following reasons:

1. Their low genetic barrier for resistance;
2. EFV is less well tolerated than the Recommended regimens; and
3. In a randomized controlled trial that compared RPV and EFV, the rate of virologic failure among participants with high pretreatment viral loads (>100,000 copies/mL) or low CD4 counts (<200 cells/mm^3) was higher among the RPV-treated participants.

Efavirenz (EFV)

Efficacy 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. In clinical trials, EFV-based regimens in ART-naive patients have demonstrated superiority or noninferiority to several comparator regimens.

- In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[91]
- In the ECHO and 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 was more frequent with RPV failure.[92]
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.[79]

Some regimens have demonstrated superiority to EFV, based primarily on fewer discontinuations because of adverse events:

- In the SINGLE trial, a DTG-based regimen was superior to EFV at the primary endpoint of viral suppression at week 48.[20]
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks.[51] RAL was superior to EFV at 4 and 5 years,[54,84] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
- In the open-label STaR trial, participants with baseline viral loads ≤100,000 copies/mL had higher rates of treatment success on RPV than on EFV.[93]

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.[94] Study drug-related adverse events were less frequent in the EFV 400 mg group than in the 600 mg group. Although there were fewer

self-reported CNS events in the 400 mg group, the groups had similar rates of psychiatric events. Unlike the 600 mg dose of EFV, the 400 mg dose is not approved for initial treatment, it is not coformulated in a fixed-dose combination tablet, and data for its use in pregnancy and in patients with TB/HIV coinfection are lacking.

Adverse Effects:

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, and depression), which resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur. An analysis of four AIDS Clinical Trial Group (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.[95] This association, however, was not found in analyses of three large observational cohorts,[96,97] or in a retrospective cohort study that used U.S. administrative pharmacy claims data.[98]
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.[99,100] Consider an alternative therapy 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 tablet and in a fixed-dose combination tablet of EFV/TDF/FTC that allows for once-daily dosing.
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6 and therefore may potentially interact with other drugs using the same pathways (see Tables 18b, 19a, and 19b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of neural tube defects have been reported after first trimester exposure in humans.[101] A link between EFV and birth defects in humans has not been supported in meta-analyses (see the Perinatal Guidelines).[102]
- Because EFV has been associated with depression and suicidality, screening for antenatal and postpartum depression in women with HIV who are taking a regimen that includes EFV is recommended.

The Panel's Recommendations:

- Given the availability of regimens with fewer treatment-limiting adverse events and also with noninferior or superior efficacy, the Panel classifies EFV/TDF/FTC **(BI)** or EFV plus TAF/FTC **(BII)** as Recommended Initial Regimens in Certain Clinical Situations.
- EFV at a reduced dose has not been studied in the U.S. population, in pregnant women, or in patients with TB/HIV coinfection. The Panel **cannot recommend** the use of reduced-dose EFV.

Rilpivirine (RPV)

RPV is an NNRTI approved for use in combination with NRTIs for ART-naive patients with pretreatment viral loads <100,000 copies/mL.

Efficacy in Clinical Trials:

Two phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.[92] At 96 weeks, the following findings were reported:

- RPV was noninferior to EFV overall.
- Among participants with a pre-ART viral load >100,000 copies/mL, more RPV-treated participants than EFV-treated participants experienced virologic failure. Moreover, in this subgroup of participants with

virologic failure, NNRTI and NRTI resistance was more frequently identified in those treated with RPV.

- 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 fixed-dose combinations of RPV/TDF/FTC and EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks[103] were similar to the findings reported at 48 weeks.[93]

- 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. In 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 fixed-dose combination tablet of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence study. In this study, participants taking the coformulated drug had plasma concentrations of RPV, FTC, and TAF 25 mg that were similar to concentrations seen in participants who received RPV as the single-tablet formulation and TAF/FTC when given as part of the fixed-dose combination of EVG/c/TAF 10 mg/FTC.[45]

Adverse Effects:

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

Other Factors and Considerations:

- RPV is formulated both as a single-drug tablet and in fixed-dose combination tablets with TAF/FTC and with TDF/FTC. Among available single-tablet regimens, RPV/TAF/FTC is the smallest tablet.
- RPV/TAF/FTC and RPV/TDF/FTC are given once daily, and must be administered with a meal (containing at least 390 kcal).
- 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, and should be used with caution in those receiving H2 antagonists or antacids (see 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 Interactions).
- At higher than 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 load <100,000 copies/mL and CD4 count >200 cells/mm^3.

- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

Protease Inhibitor-Based Regimens

Summary

FDA-approved PIs include ATV, ATV/c, DRV, DRV/c, FPV, IDV, LPV/r, nelfinavir (NFV), RTV, saquinavir (SQV), and tipranavir (TPV). PI-based regimens with PK enhancement have demonstrated virologic potency, durability in treatment-naive patients, and a high genetic barrier to resistance. Few or no PI mutations are detected when a patient's first PI-based regimen fails, which is not the case with NNRTI- and some INSTI-based regimens.[104,105] For this reason, PI-based regimens may be useful for patients at risk for intermittent therapy due to poor adherence. All PIs (PK-enhanced by either RTV or COBI) inhibit the CYP3A4 isoenzyme, which may lead to significant drug-drug interactions (see Drug Interactions). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of Recommended PIs are listed in Table 8 and Appendix B, Table 3.

PIs that are recommended for use in ART-naive patients should have proven virologic efficacy, once-daily dosing, a low pill count, and good tolerability. On the basis of these criteria, the Panel considers once-daily DRV/r, DRV/c, ATV/c, or ATV/r together with two NRTIs as PI-based regimen options in the category of Recommended Initial Regimens in Certain Clinical Situations. In a large, randomized controlled trial comparing DRV/r, ATV/r, and RAL, all in combination with TDF/FTC, all three regimens achieved similar virologic suppression rates; however, the proportion of patients who discontinued their assigned treatment because of adverse effects, mainly hyperbilirubinemia, was greater in the ATV/r arm than in the other two arms.[7]

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, while this was not seen with ATV.[12-14,106] Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens compared with other regimens.[16] Further study is needed.

LPV/r has twice the daily dose of RTV as other PI/r regimens and is associated with more metabolic complications and gastrointestinal side effects than PK-enhanced ATV or DRV. The Panel no longer recommends LPV/r plus two NRTIs as a regimen for initial therapy, given the availability of other PIs coformulated with PK enhancers that can be given once daily and the accumulation of experience with other ART regimens with fewer toxicities. DRV/r plus twice daily RAL or LPV/r plus 3TC are regimens to be considered when ABC, TAF, or TDF cannot be used (see below). Compared to other PIs, FPV/r, unboosted ATV, and SQV/r have disadvantages such as greater pill burden, lower efficacy, or increased toxicity, and thus are not included as options for initial therapy.

Recommended Protease Inhibitor-Based Regimen

Darunavir/Ritonavir (DRV/r)

Efficacy in Clinical Trials:

- The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r (800/200 mg once daily or 400/100 mg twice daily), both in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at week 48,[49] and superior at week 192.[107] Among participants with baseline HIV RNA levels >100,000 copies/mL, virologic response rates were lower in the LPV/r arm than in the DRV/r arm.

- The FLAMINGO study compared DRV/r with DTG, each in combination with two NRTIs, in 488 ART-naive participants. The rate of virologic suppression at week 96 was significantly greater among those who received DTG than in those who received DRV/r. The excess failure observed in the DRV/r group was primarily related to a higher rate of virologic failure among those with a viral load >100,000 copies/mL and secondarily due to more drug discontinuations in the DRV/r group.[8]
- ACTG A5257, a large randomized open-label trial, compared ATV/r with DRV/r or RAL, 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.[7]

Adverse Effects:

- Patients starting DRV/r may develop a skin rash, which is usually mild-to-moderately severe 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. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[7] The likelihood of developing metabolic syndrome was equivalent between the three arms, although a larger increase in waist circumference was observed in participants assigned to the RAL arm than in those in the DRV/r arm at 96 weeks ($P \leq 0.02$).[108]
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease.[106]

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 who did or did not have a history of sulfonamide allergy. Most patients with sulfonamide allergy are able to tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, and may lead to significant interactions with other medications metabolized through this same pathway (see 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 TDF/FTC **(AI)**, with TAF/FTC **(AII)**, or with ABC/3TC **(BII)** as Recommended Initial Regimens in Certain Clinical Situations.

Darunavir/Cobicistat (DRV/c)

A combination of DRV 800 mg with COBI 150 mg is bioequivalent to DRV 800 mg with RTV 100 mg in healthy volunteers based on the maximum concentration and area under the concentration time curve for DRV.[109] Because the minimum concentration (C_{min}) of DRV combined with COBI was 31% lower than that with DRV combined with RTV, bioequivalence for the C_{min} was not achieved.[110]

Efficacy in Clinical Trials:

- In a single-arm trial of treatment-naive (94%) and treatment-experienced (6%) patients, the coformulated DRV/c 800/150 mg tablet was evaluated in combination with two investigator-selected NRTIs (99% of participants were given TDF/FTC). At week 48, 83% of treatment-naive participants achieved HIV RNA <50 copies/mL; 5% of participants discontinued treatment because of adverse events.[111]
- A phase 2 study of coformulated DRV/c plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% and 74%, respectively) in treatment-naive patients.[25] Less proteinuria and less change in bone mineral density were observed in the TAF arm.

Adverse Effects:

- The most common treatment-emergent adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease;[106] data on DRV/c are too limited to draw conclusions.

Other Factors:

- DRV 800 mg and COBI 150 mg is available as a coformulated tablet.

The Panel's Recommendations:

- On the basis of the bioequivalence study and the single-arm trial, the Panel recommends DRV/c plus TAF/FTC or TDF/FTC **(BII)** and DRV/c plus ABC/3TC **(BIII)** as Recommended Initial Regimens in Certain Clinical Situations.
- DRV/c plus TDF/FTC **is not recommended** for patients with 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:

- The CASTLE study compared once-daily ATV/r (300/100 mg) with twice-daily LPV/r (400/100 mg), each in combination with TDF/FTC. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 96 weeks.[112]
- The ACTG A5202 study compared open-label ATV/r and EFV, each given in combination with placebo-controlled TDF/FTC or ABC/3TC. Efficacy was similar in the ATV/r and EFV groups.[91] 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.[113]
- In a study comparing ATV/r plus TDF/FTC to EVG/c/TDF/FTC, virologic suppression rates through 144 weeks were similar in the two groups.[80] A phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.[9] At week 48, the virologic suppression rate in the EVG/c arm was superior to the ATV/r arm. Nineteen women in the PI arm discontinued therapy because of adverse events, compared to five women in the INSTI arm.
- In ACTG A5257, a significantly higher proportion of patients in the ATV/r arm discontinued randomized treatment because of adverse events, mostly for 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.[7]
- 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.[114] Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentage of treatment-discontinuing adverse events and changes in serum creatinine and indirect bilirubin levels were comparable.[115]
- In a phase 3 trial, 499 ART-naive women were randomized to either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, DTG was found to be noninferior to ATV/r in rate of virologic suppression (<50 copies/mL) and fewer drug-related adverse events occurred in the DTG arm.[72]

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.[116]

- Nephrolithiasis,[117-119] nephrotoxicity,[15] and cholelithiasis[120] have also been reported in patients who received ATV, with or without RTV.
- 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 and 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 18a 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 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, while this was not seen with ATV.[12-14,106] Another study of an observational cohort of predominantly male participants found a lower rate of CV events in participants receiving ATV-containing regimens compared with participants receiving other regimens.[16] Further study is needed.

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TAF/FTC **(BII)** or TDF/FTC **(BI)** as Recommended Initial Regimens in Certain Clinical Situations.
- ATV/r or ATV/c may be used with ABC/3TC in patients whose pre-ART HIV RNA <100,000 copies/mL (**CI** for ATV/r and **CIII** for ATV/c).
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

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

All currently Recommended ARV regimens consist of two NRTIs plus a third active drug. This strategy, however, may not be possible or optimal in all patients. In some situations, it may be necessary to avoid ABC, TAF, and TDF, such as in the case of a patient who is HLA-B*5701–positive or at high risk of cardiovascular disease and with significant renal impairment. Based on these concerns, several clinical studies have evaluated strategies using initial regimens that avoid two NRTIs or the NRTI drug class altogether. 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 with Good Supporting Evidence

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

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive either twice-daily RAL or once-daily TDF/FTC, both with DRV/r (800/100 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 count <200 cells/mm^3, however, there were more failures in the two-drug arm; a trend towards more failure was also observed for those with pretreatment HIV RNA ≥100,000 copies/mL.[121] 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.[122,123]
- 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/uL and CD4 counts >200 cells/mm^3, and only in those patients who cannot take ABC, TAF, or TDF **(CI)**.

Lopinavir/Ritonavir plus Lamivudine (LPV/r plus 3TC)

- In the GARDEL study, 426 ART-naive patients were randomized to receive twice-daily LPV/r plus either open-label 3TC (twice daily) or two NRTIs selected by the study investigators. At 48 weeks, a similar number of patients in each arm had HIV RNA <50 copies/mL, meeting the study's noninferiority criteria. The LPV/r plus 3TC regimen was better tolerated than the LPV/r plus two NRTI regimen.[124]
- This regimen is used infrequently given the requirement of twice-daily dosing, the relatively high pill burden (a total of 5–6 tablets per day), and the side effect profile of LPV/r. In view of the above limitations, the Panel recommends that LPV/r plus 3TC be considered for use only in patients who cannot take ABC, TAF, or TDF and in whom other alternatives cannot be used **(CI)**.

Selected Strategies That Are Under Evaluation and Not Yet Recommended

Several other treatment regimens for ART-naive patients who cannot use ABC, TAF, and TDF are currently under investigation. As the current data supporting these regimens are limited to single-arm studies or interim analyses of ongoing trials, these regimens cannot yet be recommended. However, some experts may consider these regimens when a patient cannot safely receive ABC, TAF, or TDF. If these treatment strategies are used, patients should be closely monitored to assure viral suppression is achieved and maintained. Two selected strategies are listed below.

Dolutegravir plus Lamivudine (DTG plus 3TC)

- The PADDLE trial was a small, single-arm study of DTG plus 3TC in 20 ART-naive adults with baseline HIV RNA <100,000 copies/mL. At 48 weeks, 18/20 (90%) subjects achieved HIV RNA <50 copies/mL.[125] Fifteen of these 18 participants completed 96 weeks of treatment and maintained HIV RNA <50 copies/mL.[126]
- The ACTG A5353 trial evaluated this same regimen in a single-arm trial that included ART-naive participants with a baseline HIV RNA of up to 500,000 copies/mL and no genotypic NRTI, INSTI, or PI resistance. The trial enrolled 120 participants; 37 (30.8%) participants had a baseline HIV RNA >100,000 copies/mL. At week 24, 90% of participants had HIV RNA <50 copies/mL; there were similar response rates in participants with baseline HIV RNA >100,000 copies/mL and ≤100,000 copies/mL (89% and 90%, respectively). Three participants experienced virologic failure, all of whom had suboptimal adherence (one developed an integrase gene-associated mutation).[127]
- Two phase 3 trials (GEMINI 1 and 2) comparing DTG plus 3TC to a three-drug regimen of DTG plus TDF/FTC in treatment-naive people with HIV are currently ongoing.

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

- In the ANDES trial, 145 participants were randomized 1:1 to receive either open-label dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus 3TC/TDF. The median baseline HIV RNA was 4.5 $\log_{10}$ copies, and 24% of subjects had HIV RNA >100,000 copies/mL. The trial is still ongoing, but an intention-to-treat snapshot analysis performed at week 24 showed that 71/75 (95%) subjects in the dual-therapy arm and 68/70 (97%) subjects in the triple-therapy arm achieved HIV RNA <400 copies/mL. By week 24, four subjects in the dual-therapy arm and one subject in the triple-therapy arm had discontinued treatment for reasons other than virologic failure. Virologic failure was documented in one subject in the triple-therapy arm. The investigators intend to enroll an additional 190 patients to power the study for a noninferiority assessment at the primary (week 48) virologic endpoint.[128]

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 4)

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	• May cause life-threatening HSRs in patients 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 EVG/c or RPV • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than after initiation of TDF/FTC • Approved for patients with eGFR ≥30 mL/min	• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids.
	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 with ABC/3TC in patients with baseline viral load ≥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 • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreases BMD more than other NRTI combinations
INSTI	**DTG**	• Higher barrier to resistance than EVG or RAL • Coformulated with ABC and 3TC • No food requirement • No 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 18d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function • UGT substrate; potential for drug interactions (see Table 18d) • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 4)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, continued	**EVG/c**	• Coformulated with TDF/FTC or TAF/FTC • Compared with ATV/r, causes smaller increases in total and LDL cholesterol	• EVG/c/TDF/FTC is only recommended 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 18d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function. • Lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Food requirement • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
	RAL	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions • Favorable lipid profile	• Lower genetic barrier to resistance than boosted PI- 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 fixed-dose combination 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 18d. • UGT substrate; potential for drug interactions (see Table 18d) • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 4)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
NNRTIs	**EFV**	• Coformulated with TDF/FTC • Long-term clinical experience • EFV-based regimens (except for EFV + 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 • Teratogenic in nonhuman primates • Dyslipidemia • Rash • QTc interval prolongation; consider an alternative to EFV in patients taking medications with known risk of causing TdP, or in those at higher risk of TdP. • Transmitted resistance 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 18b and 19a) • 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 size than other coformulated ARV drugs • Compared with EFV: • Fewer CNS adverse effects • Fewer lipid effects • Fewer rashes	• **Not recommended** in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm^3 because of higher rate of virologic failure in these patients • Depression and suicidality • QTc interval prolongation; consider an alternative to RPV in patients taking medications with known risk of causing TdP, or in those at higher risk of TdP. • Rash • Transmitted resistance more common than with PIs and INSTIs • More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimen containing EFV and 2 NRTIs • Potential for CYP450 drug interactions (see Tables 18b and 19a) • Meal requirement (>390 kcal) • Requires acid for adequate absorption • Contraindicated with PPIs • Use with H2 antagonists or antacids with caution (see Table 18a for detailed dosing information).
PIs	**ATV/c** or **ATV/r**	• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure 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, while this has not been seen with ATV. Further study is needed. See text for discussion.	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice • Food requirement • Absorption depends on food and low gastric pH (see Table 18a for interactions with H2 antagonists, antacids, and PPIs) • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 18a)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 4)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
PIs, continued	**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 • Less long-term clinical experience than for ATV/r • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.
	DRV/c or **DRV/r**	• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with PK-enhanced PIs	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table18a) • Increased CV risk in one observational cohort study
	DRV/c (Specific considerations)	• Coformulated tablet	• Less long-term clinical experience than for DRV/r • 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 • Approval primarily based on PK data comparable to that for DRV/r rather than on trials comparing the efficacy of DRV/c and DRV/r • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.
	LPV/r	• Only RTV-coformulated PI • No food requirement	• Requires 200 mg per day of RTV • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or in patients receiving other drugs with similar effect. • Possible nephrotoxicity • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 18a)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI or c = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; EFV = efavirenz; EVG = elvitegravir; 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 = lopinavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV or r = ritonavir; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TdP = torsades de pointes; TEN = toxic epidermal necrosis; UGT = uridine diphosphate glucuronosyltransferase

Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy page 1 of 2

ARV Components or Regimens	Reasons for Not Recommending as Initial Therapy
NRTIs	
ABC/3TC/ZDV (Coformulated) As triple-NRTI combination regimen	• Inferior virologic efficacy
ABC/3TC/ZDV + TDF As quadruple-NRTI combination regimen	• Inferior virologic efficacy
d4T + 3TC	• Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)
ddI + 3TC (or FTC)	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicities such as pancreatitis and peripheral neuropathy
ddI + 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
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 (three 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 + 2 NRTIs	• Higher pill burden than other PI-based regimens • Higher ritonavir dose than other PI-based regimens • GI intolerance
NFV	• Inferior virologic efficacy • Diarrhea
RTV as sole PI	• High pill burden • GI intolerance • Metabolic toxicity

Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy page 2 of 2

ARV Components or Regimens	Reasons for Not Recommending as Initial Therapy
PIs, continued	
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
CCR5 Antagonist	
MVC	• Requires testing for CCR5 tropism before initiation of therapy • No virologic benefit when compared with other recommended regimens • Requires twice-daily dosing

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; COBI or c = cobicistat; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RTV or r = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

References

1. Moore RD, Bartlett JG. Dramatic decline in the HIV-1 RNA level over calendar time in a large urban HIV practice. *Clin Infect Dis*. 2011;53(6):600-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844006.

2. Gill VS, Lima VD, Zhang W, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. *Clin Infect Dis*. 2010;50(1):98-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19951169.

3. Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PloS one*. 2014;9(5):e97482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24830290.

4. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25890673.

5. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *The Lancet HIV*. 2016;3(4):e158-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27036991.

6. Wohl D, Thalme A, Finlayson R, et al. Renal safety of tenofovir alafenamide in patients at high risk of kidney disease. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: http://www.croiconference.org/sessions/renal-safety-tenofovir-alafenamide-patients-high-risk-kidney-disease.

7. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25285539.

8. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *The Lancet HIV*. 2015;2(4):e127-136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26424673.

9. Squires K, Kityo C, Hodder S, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected

women (WAVES): a randomised, controlled, double-blind, phase 3 study. *The Lancet HIV*. 2016;3(9):e410-e420. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27562742.

10. Stein JH, Ribaudo HJ, Hodis HN, et al. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness. *AIDS*. 2015;29(14):1775-1783. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26372383.

11. de Saint-Martin L, Bressollette L, Perfezou P, et al. Impact of atazanavir-based HAART regimen on the carotid intima-media thickness of HIV-infected persons: a comparative prospective cohort. *AIDS*. 2010;24(18):2797-2801. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21063175.

12. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*. 2010;170(14):1228-1238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20660842.

13. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20039804.

14. Monforte AD, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events. *AIDS*. 2013;27(3):407-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23291539.

15. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis*. 2013;207(9):1359-1369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23382571.

16. LaFleur J, Bress AP, Rosenblatt L, et al. Cardiovascular outcomes among HIV-infected veterans receiving atazanavir. *AIDS*. 2017;31(15):2095-2106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28692532.

17. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19952143.

18. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *Journal of Acquired Immune Deficiency Syndromes*. 2010;55(1):49-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20431394.

19. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23(12):1547-1556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19542866.

20. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369(19):1807-1818. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24195548.

21. Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis*. 2011;204(8):1191-1201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21917892.

22. Arribas JR, Thompson M, Sax PE, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2017;75(2):211-218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28282300.

23. Rijnders BJ, Post FA, Rieger A, et al. Longer-term renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: http://www.croiconference.org/sessions/longer-term-renal-safety-tenofovir-alafenamide-vs-tenofovir-disoproxil-fumarate.

24. Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *Journal of Acquired Immune Deficiency Syndromes*. 2016;72(1):58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26829661.

25. Mills A, Crofoot GJ, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. *Journal of Acquired Immune*

Deficiency Syndromes. 2015;69(4):439-445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25867913.

26. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B coinfected adults. *Journal of Acquired Immune Deficiency Syndromes*. 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27171740.

27. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis*. 2004;39(7):1038-1046. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15472858.

28. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *Journal of Acquired Immune Deficiency Syndromes*. 2004;35(1):22-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14707788.

29. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir / ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS*. 2004;18(11):1529-1537. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15238771.

30. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18444831.

31. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18256392.

32. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18387667.

33. The SMART/INSIGHT and the D:A:D Study Groups TSIatDADSG. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22(14):F17-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753925.

34. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med*. 2010;11(2):130-136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19682101.

35. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS*. 2011;25(10):1289-1298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21516027.

36. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *Journal of Acquired Immune Deficiency Syndromes* . 2011;57(3):245-253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21499115.

37. Palella FJ, Althoff KN, Moore R, et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD. Presented at: Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, Washington. Available at: http://www.croiconference.org/sessions/abacavir-use-and-risk-myocardial-infarction-na-accord.

38. Young J, Xiao Y, Moodie EE, et al. Effect of cumulating exposure to abacavir on the risk of cardiovascular disease events in patients from the Swiss HIV Cohort Study. *Journal of Acquired Immune Deficiency Syndromes*. 2015;69(4):413-421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25932884.

39. Marcus JL, Neugebauer RS, Leyden WA, et al. Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. *Journal of Acquired Immune Deficiency Syndromes*. 2016;71(4):413-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26536316.

40. Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med*. 2016;14:61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27036962.

41. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased

risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *Journal of Acquired Immune Deficiency Syndromes*. 2009;51(1):20-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19282778.

42. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2011;53(1):84-91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21653308.

43. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis*. 2011;52(7):929-940. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21427402.

44. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *Journal of Acquired Immune Deficiency Syndromes*. 2012;61(4):441-447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22932321.

45. Zack J, Chuck S, Chu H, et al. Bioequivalence of the rilpivirine/emtricitabine/tenofovir alafenamide single-tablet regimen. *Journal of Bioequivalence & Bioavailability*. 2016;8(2):49-54. Available at: http://www.omicsonline.org/open-access/bioequivalence-of-the-rilpivirineemtricitabinetenofovir-alafenamidesingletablet-regimen-jbb-1000266.pdf.

46. Cassetti I, Madruga JV, Suleiman JM, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naive HIV-1-infected patients. *HIV Clinical Trials*. 2007;8(3):164-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17621463.

47. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Research and Human Retroviruses*. 2007;23(12):1505-1514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18160008.

48. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646-655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18722869.

49. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389-1397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18614861.

50. Smith KY, Weinberg WG, Dejesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT. *AIDS Res Ther*. 2008;5:5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18373851.

51. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19647866.

52. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. 2012;379(9835):2429-2438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22748590.

53. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379(9835):2439-2448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22748591.

54. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clinical Trials*. 2012;13(4):228-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22849964.

55. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24074642.

56. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis*.

2003;36(8):1070-1073. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12684922.

57. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis*. 2006;42(2):283-290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16355343.

58. Gervasoni C, Meraviglia P, Landonio S, et al. Low body weight in females is a risk factor for increased tenofovir exposure and drug-related adverse events. *PloS one*. 2013;8(12):e80242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24312465.

59. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS*. 2009;23(15):1971-1975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19696652.

60. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *Journal of Acquired Immune Deficiency Syndromes*. 2006;43(3):278-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17079992.

61. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 2008;197(1):102-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18171292.

62. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clinical Pharmacology and Therapeutics*. 2008;83(2):265-272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17597712.

63. Gilead. Stribild package insert. 2017. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/hiv/stribild/stribild_pi.pdf.

64. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. 2010;51(8):963-972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20828304.

65. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis*. 2011;203(12):1791-1801. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21606537.

66. Perrot S, Aslangul E, Szwebel T, Caillat-Vigneron N, Le Jeunne C. Bone pain due to fractures revealing osteomalacia related to tenofovir-induced proximal renal tubular dysfunction in a human immunodeficiency virus-infected patient. *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*. 2009;15(2):72-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19265350.

67. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the *HIV Med*icine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(9):e96-138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25234519.

68. Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *Journal of Acquired Immune Deficiency Syndromes*. 2015;70(5):515-519. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26262777.

69. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24698485.

70. Feinberg J, Clotet B, Khuong-Josses MA, et al. Once-daily dolutegravir (DTG) is superior to darunavir/ritonavir (DRV/r) in antiretroviral-naive adults: 48 week results from FLAMINGO (ING114915). Presented at: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy. 2013. Denver, CO.

71. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. *Journal of the International AIDS Society*. 2014;17(4 Suppl 3):19490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25393999.

72. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus

ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *The Lancet HIV*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28729158.

73. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. 2015;29(13):1723-1725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26372287.

74. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. 2008;22(14):1890-1892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753871.

75. Penafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *The Journal of Antimicrobial Chemotherapy*. 2017;72(6):1752-1759. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28333231.

76. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med*. 2017;18(1):56-63. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27860104.

77. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. *Journal of Acquired Immune Deficiency Syndromes*. 2017;74(4):423-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27984559.

78. Kheloufi F, Boucherie Q, Blin O, Micallef J. Neuropsychiatric events and dolutegravir in HIV patients: a worldwide issue involving a class effect. *AIDS*. 2017;31(12):1775-1777. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28700395.

79. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2014;65(3):e118-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24256630.

80. Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2014;65(3):e121-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24346640.

81. Gilead. Genvoya package insert. 2017. Available at: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf.

82. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clinical Pharmacology and Therapeutics*. 2009;85(1):64-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18815591.

83. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *Journal of Acquired Immune Deficiency Syndromes*. 2012;61(1):32-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22732469.

84. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *Journal of Acquired Immune Deficiency Syndromes*. 2013;63(1):77-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23412015.

85. Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. *The Lancet HIV*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28918877.

86. Merck Sharp & Dohme Corp. Isentress package insert. 2017. Available at: http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf. Accessed: Sep 20, 2017.

87. Gray J, Young B. Acute onset insomnia associated with the initiation of raltegravir: a report of two cases and literature review. *AIDS Patient Care and STDs*. 2009;23(9):689-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19663717.

88. Snedecor SJ, Khachatryan A, Nedrow K, et al. The prevalence of transmitted resistance to first-generation non-

nucleoside reverse transcriptase inhibitors and its potential economic impact in HIV-infected patients. *PloS one*. 2013;8(8):e72784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23991151.

89. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *Journal of Acquired Immune Deficiency Syndromes*. 2012;60(1):33-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22343174.

90. Janssen. Edurant package insert. 2017. Available at: http://www.edurant.com/shared/prescribing-information-edurant.pdf. Accessed: Oct 6, 2017.

91. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011;154(7):445-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21320923.

92. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS*. 2013;27(6):939-950. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23211772.

93. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. *AIDS*. 2014;28(7):989-997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24508782.

94. Group ES. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24522178.

95. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med*. 2014;161(1):1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24979445.

96. Smith C, Ryom L, Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. *Journal of the International AIDS Society*. 2014;17(4 Suppl 3):19512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25394021.

97. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. *Journal of the International AIDS Society*. 2014;17:19214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25192857.

98. Nkhoma ET, Coumbis J, Farr AM, et al. No evidence of an association between efavirenz exposure and suicidality among HIV patients initiating antiretroviral therapy in a retrospective cohort study of real world data. *Medicine (Baltimore)*. 2016;95(3):e2480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26817882.

99. Bristol-Myers Squibb. Sustiva package insert. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020972s049-021360s038lbl.pdf. Accessed: Sep 20, 2017.

100. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6*6*6 allele carriers. *J Cardiovasc Electrophysiol*. 2016;27(10):1206-1213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27333947.

101. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16(2):299-300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11807320.

102. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25(18):2301-2304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21918421.

103. van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. *AIDS*. 2016;30(2):251-259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26684822.

104. Lathouwers E, De Meyer S, Dierynck I, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther*. 2011;16(1):99-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21311113.

105. Soriano V, Arasteh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther*. 2011;16(3):339-348. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21555816.

106. Ryom L, Lundgren JD, El-Sadr WM, et al. Association between cardiovascular disease and contemporarily used protease inhibitors. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington. Available at: http://www.croiconference.org/sessions/association-between-cardiovascular-disease-contemporarily-used-protease-inhibitors.

107. Orkin C, Dejesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med*. 2013;14(1):49-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23088336.

108. Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis*. 2015;60(12):1842-1851. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25767256.

109. Gilead. Tybost package insert. 2017. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/hiv/tybost/tybost_pi.pdf. Accessed: Sep 20, 2017.

110. Janssen Therapeutics. Prezcobix package insert. 2017. Available at: https://www.prezcobix.com/sites/www.prezcobix.com/files/prescribing-information-prezcobix.pdf. Accessed: Sep 20, 2017.

111. Tashima K, Crofoot G, Tomaka FL, et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. *AIDS Res Ther*. 2014;11:39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25926858.

112. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *Journal of Acquired Immune Deficiency Syndromes*. 2010;53(3):323-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20032785.

113. Smith KY, Tierney C, Mollan K, et al. Outcomes by sex following treatment initiation with atazanavir plus ritonavir or efavirenz with abacavir/lamivudine or tenofovir/emtricitabine. *Clin Infect Dis*. 2014;58(4):555-563. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24253247.

114. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. *J Infect Dis*. 2013;208(1):32-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23532097.

115. Gallant JE, Koenig E, Andrade-Villanueva JF, et al. Brief report: cobicistat compared with ritonavir as a pharmacoenhancer for atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate: week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2015;69(3):338-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26181707.

116. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and atazanavir prescribing. *Clinical Pharmacology and Therapeutics*. 2016;99(4):363-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26417955.

117. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS*. 2007;21(9):1215-1218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17502736.

118. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS*. 2011;25(13):1671-1673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21716074.

119. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis*. 2012;55(9):1262-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22820542.

120. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. *Clin Infect Dis*. 2012;55(9):1270-1272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22820540.

121. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014;384(9958):1942-1951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25103176.

122. Taiwo B, Zheng L, Gallien S, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS*. 2011;25(17):2113-2122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21857490.

123. Bedimo RJ, Drechsler H, Jain M, et al. The RADAR study: week 48 safety and efficacy of RAltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Impact on bone health. *PloS one*. 2014;9(8):e106221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25170938.

124. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. 2014;14(7):572-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24783988.

125. Cahn P, Rolon MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. *Journal of the International AIDS Society*. 2017;20(1):1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28537061.

126. Figueroa MI, Rolón MJ, Patterson P, Gun A, Cahn P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naive patients: 96 week results of the PADDLE trial. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197.

127. Taiwo BO, Zheng L, Nyaku AN, et al. ACTG A5353: a pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197.

128. Sued O, Figueroa MI, Gun A, et al. Dual therapy with darunavir/ritonavir plus lamivudine for HIV-1 treatment initiation: week 24 results of the randomized ANDES study. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197.

What Not to Use (Last updated October 17, 2017; last 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 18a and 18d).

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 below these CD4 count thresholds increases the risk of symptomatic, and sometimes life-threatening, hepatic events.[24-26] Patients with CD4 counts above these thresholds due to ART can safely switch to NVP **(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.

References

1. Katlama C, Ingrand D, Loveday C, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA*. Jul 10 1996;276(2):118-125. Available at https://www.ncbi.nlm.nih.gov/pubmed/8656503.
2. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. *AIDS*. Jan 30 2008;22(3):385-393. Available at https://www.ncbi.nlm.nih.gov/pubmed/18195565.
3. Swindells S, DiRienzo AG, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA*. Aug 16 2006;296(7):806-814. Available at https://www.ncbi.nlm.nih.gov/pubmed/16905786.
4. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS*. Jan 16 2010;24(2):223-230. Available at https://www.ncbi.nlm.nih.gov/pubmed/20010070.
5. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. Sep 24

2010;24(15):2365-2374. Available at https://www.ncbi.nlm.nih.gov/pubmed/20802297.

6. Stohr W, Dunn DT, Arenas-Pinto A, et al. Factors associated with virological rebound in HIV-infected patients receiving protease inhibitor monotherapy. *AIDS*. Nov 13 2016;30(17):2617-2624. Available at https://www.ncbi.nlm.nih.gov/pubmed/27456983.

7. Oldenbuettel C, Wolf E, Ritter A, et al. Dolutegravir monotherapy as treatment de-escalation in HIV-infected adults with virological control: DoluMono cohort results. *Antivir Ther.* 2017;22(2):169-172. Available at https://www.ncbi.nlm.nih.gov/pubmed/27588613.

8. Brenner BG, Thomas R, Blanco JL, et al. Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors. *J Antimicrob Chemother*. Jul 2016;71(7):1948-1953. Available at https://www.ncbi.nlm.nih.gov/pubmed/27029845.

9. Hirsch M, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis*. Sep 1999;180(3):659-665. Available at https://www.ncbi.nlm.nih.gov/pubmed/10438352.

10. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis*. Dec 1 2005;192(11):1921-1930. Available at https://www.ncbi.nlm.nih.gov/pubmed/16267763.

11. Bartlett JA, Johnson J, Herrera G, et al. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr*. Nov 1 2006;43(3):284-292. Available at https://www.ncbi.nlm.nih.gov/pubmed/16967040.

12. Barnas D, Koontz D, Bazmi H, Bixby C, Jemsek J, Mellors JW. Clonal resistance analyses of HIV type-1 after failure of therapy with didanosine, lamivudine and tenofovir. *Antivir Ther.* 2010;15(3):437-441. Available at https://www.ncbi.nlm.nih.gov/pubmed/20516563.

13. Food and Drug Administration. Caution issued for HIV combination therapy with Zerit and Videx in pregnant women. *HIV Clin.* 2001;13(2):6. Available at https://www.ncbi.nlm.nih.gov/pubmed/11810823.

14. Kearney BP, Sayre JR, Flaherty JF, Chen SS, Kaul S, Cheng AK. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. *J Clin Pharmacol.* Dec 2005;45(12):1360-1367. Available at https://www.ncbi.nlm.nih.gov/pubmed/16291710.

15. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis.* Apr 15 2003;36(8):1082-1085. Available at https://www.ncbi.nlm.nih.gov/pubmed/12684925.

16. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet*. Jul 3-9 2004;364(9428):65-67. Available at https://www.ncbi.nlm.nih.gov/pubmed/15234858.

17. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS*. Mar 24 2005;19(6):569-575. Available at https://www.ncbi.nlm.nih.gov/pubmed/15802975.

18. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS*. Jan 28 2005;19(2):213-215. Available at https://www.ncbi.nlm.nih.gov/pubmed/15668550.

19. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS*. Jul 22 2005;19(11):1183-1188. Available at https://www.ncbi.nlm.nih.gov/pubmed/15990571.

20. Podzamczer D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther.* 2005;10(1):171-177. Available at https://www.ncbi.nlm.nih.gov/pubmed/15751775.

21. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. Apr 17 2004;363(9417):1253-1263. Available at https://www.ncbi.nlm.nih.gov/pubmed/15094269.

22. Tibotec Inc. Intelence package insert. 2009. Available at http://www.intelence.com/shared/product/intelence/prescribing-information.pdf.

23. Bethell R, Adams J, DeMuys J, et al. Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SPD754. Presented at Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, California.

24. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):538-539. Available at https://www.ncbi.nlm.nih.gov/pubmed/15021321.

25. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis*. Mar 15 2005;191(6):825-829. Available at https://www.ncbi.nlm.nih.gov/pubmed/15717255.

26. Boehringer Ingelheim. Dear Health Care Professional Letter: Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE® (nevirapine). 2004.

27. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS*. Aug 24 2009;23(13):1689-1699. Available at https://www.ncbi.nlm.nih.gov/pubmed/19487907.

28. Hoggard PG, Kewn S, Barry MG, Khoo SH, Back DJ. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother*. Jun 1997;41(6):1231-1236. Available at https://www.ncbi.nlm.nih.gov/pubmed/9174176.

29. Havlir DV, Tierney C, Friedland GH, et al. In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis*. Jul 2000;182(1):321-325. Available at https://www.ncbi.nlm.nih.gov/pubmed/10882616.

Management of the Treatment-Experienced Patient

Virologic Failure (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations
• Assessing and managing a patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.
• Evaluation of virologic failure should include an assessment of adherence, drug-drug or drug-food interactions, drug tolerability, HIV RNA and CD4 T lymphocyte (CD4) cell count trends over time, ART history, and prior and current drug-resistance testing 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 **(AII)**. Even if more than 4 weeks have elapsed since ARVs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII)**.
• 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 below the lower limits of detection of currently used assays) **(AI)**.
• A new regimen should include at least two, and preferably three, fully active agents **(AI)**. A fully active agent is one that is expected to have uncompromised activity on the basis of the patient's ART history and his or her current and past drug-resistance testing results. A fully active agent may also have a novel mechanism of action.
• In general, adding a single ARV agent to a virologically failing regimen **is not recommended** because this may risk the development of resistance to all drugs in the regimen **(BII)**.
• For some 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 designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.
• 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.
• When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.
• Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and an increase in the risk of clinical progression. Therefore, this strategy **is not recommended** in the setting of virologic failure **(AI)**.
• Table 10 provides guidance on antiretroviral (ARV) regimen options in patients with virologic failure.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
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 currently recommended for initial therapy of patients with HIV have a high likelihood of achieving and maintaining plasma HIV RNA levels 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. Many patients with detectable viral loads have challenges adhering to treatment. Depending on their treatment histories, some of these patients may have minimal or no drug resistance; 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 an 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 this 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: Confirmed HIV RNA ≥200 copies/mL after virologic suppression.

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 <200 copies/mL.

Antiretroviral Therapy Treatment 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 do not emerge. Although not conclusive, the evidence suggests that selection of drug-resistance mutations does not occur in patients with HIV RNA levels persistently suppressed to 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 persistently low 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] Findings from a large retrospective analysis showed that, as a threshold for virologic failure, HIV RNA levels of <200 copies/mL and <50 copies/mL had the same predictive value for subsequent rebound to >200 copies/mL.[6] Two other retrospective studies also support the supposition that virologic rebound is more likely to occur in patients with viral loads >200 copies/mL than in those with low-level viremia between 50 and 199 copies/mL.[7,8] However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) can be predictive of progressive viral rebound[9,10] and can be associated with the evolution of drug resistance.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[12] This association is particularly common when HIV RNA levels are >500 copies/mL.[13] Therefore, persistent plasma HIV RNA levels ≥200 copies/mL are considered 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.[14,15] The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure.[16] Virologic failure may be associated with various patient/adherence-, HIV-, and regimen-related factors, as listed below:

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

- Comorbidities that may affect adherence (e.g., active substance abuse, 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 ARVs (i.e., may affect ability to access or continue therapy)
- Drug adverse effects
- High pill burden and/or dosing frequency

HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus documented by current or past resistance testing
- Prior treatment failure
- Innate resistance to ARVs based on tropism or the presence of HIV-2 infection/co-infection.
- Higher pretreatment HIV RNA level (some regimens may be less effective)

ARV Regimen-Related Factors

- Suboptimal pharmacokinetics (variable absorption, metabolism, or possible penetration into reservoirs)
- Suboptimal virologic potency
- Low genetic barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-nucleoside therapy, or the sequential introduction of drugs)
- Food requirements
- Adverse drug-drug interactions with concomitant medications
- Prescription errors

Managing Patients with Virologic Failure

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above listed 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. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy may differ. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be undertaken to improve virologic outcomes. Those approaches are outlined below.

Key Factors to Consider When Designing a New Antiretroviral Regimen

- Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs whose predicted activity is based on the patient's ART history, current and previous resistance testing, or a new mechanistic action **(AI)**.[9,17-26]
- Despite drug resistance, some ARV drugs may contribute partial ARV activity to a regimen and may be retained as part of a salvage regimen. These drugs may include nucleoside reverse transcriptase inhibitors (NRTIs) or protease inhibitors (PIs).[27] Other agents will likely have to be discontinued, as their continued use may lead to further accumulation of resistance mutations and jeopardize treatment options with newer drugs from the same drug class. These drugs may include enfuvirtide (T20); non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz (EFV), nevirapine (NVP), and rilpivirine (RPV); and the first-generation integrase strands transfer inhibitors (INSTIs) raltegravir (RAL) or elvitegravir (EVG).[28-30]
- Using a "new" drug that a patient has never used previously does not ensure that the drug will be fully active; there is a potential for cross-resistance among drugs from the same class.

- Archived drug-resistance mutations may not be detected by standard drug-resistance tests, particularly if testing is performed when the patient is not taking the drug in question.
- Drug potency and viral susceptibility based on cumulative genotype data are more important factors to consider when constructing a salvage regimen than the number of component drugs.
- Resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of regimen discontinuation if the patient's plasma HIV RNA level is >1,000 copies/mL **(AI)**, and possibly even if it is between 500 to 1,000 copies/mL **(BII)** (see Drug-Resistance Testing). In some patients, resistance testing should be considered even after treatment interruptions of more than 4 weeks, recognizing that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present at low levels **(CIII)**. Drug resistance is cumulative; thus, evaluate the extent of drug resistance, taking into account prior ART history and, importantly, prior genotypic or phenotypic resistance-test results. Some assays only detect resistance to NRTIs, NNRTIs, or PIs, whereas 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 experiencing failure on a fusion inhibitor **(AII)** and viral tropism tests for patients experiencing failure on a CCR5 antagonist **(BIII)** are also available (see Drug-Resistance Testing).
- Discontinuing or briefly interrupting therapy in a patient with overt or low-level viremia **is not recommended**, as it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count and increases the risk of clinical progression **(AI)**.[27,31] See Discontinuation or Interruption of Antiretroviral Therapy.
- When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV (see Hepatitis B (HBV)/HIV Coinfection).

Antiretroviral Strategies

- In general, patients who receive at least three active drugs experience better and more sustained virologic response than those receiving fewer active drugs in the regimen. These three drugs should be selected based on the patient's ART history and a review of their drug-resistance test results, both past and present.[18,19,21,22,32,33]
- Active drugs are ARVs that, based on current and previous resistance test results and ART history, are expected to have antiviral activity equivalent to that seen when there is no resistance to the specific drugs. ARVs with partial activity are those predicted to reduce HIV RNA, but to a lesser extent than when there is no underlying drug resistance.
- Active drugs may be newer members of existing drug classes that are active against HIV isolates that are resistant to older drugs in the same classes (e.g., etravirine [ETR], darunavir [DRV], and dolutegravir [DTG]).
- An active drug may also be one with a unique mechanism of action compared to prior therapy in that individual (e.g., the fusion inhibitor T20, the CCR5 antagonist maraviroc in patients with no detectable CXCR4-using virus, and some investigational ARV drugs).
- Increasing data in treatment-naive and treatment-experienced patients show that an active pharmacokinetically-enhanced PI plus one other active drug or plus several partially-active drugs will effectively reduce viral load in most patients.[34-37]
- In the presence of certain drug resistance mutations, some ARVs, such as DTG, ritonavir-boosted DRV (DRV/r), and ritonavir-boosted lopinavir (LPV/r), need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be active against a less-sensitive virus.[38,39]

Addressing Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogenous group of individuals with different ART exposure history, extents of drug resistance, duration 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 assess and address adherence and potential drug-drug interactions (including those with over-the-counter products and supplements) and drug-food interactions. Some general approaches based on level of viremia are addressed below.

- **HIV RNA above the LLOD and <200 copies/mL:** Patients who typically have these HIV RNA levels (i.e., blips) do not require a change in treatment **(AII)**.[4] Although there is no consensus on how to manage these patients, the risk of emerging resistance is believed to be relatively low. Therefore, these patients should maintain on their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes in ART in the future **(AIII)**.
- **HIV RNA ≥200 and <1,000 copies/mL:** In contrast to patients with detectable HIV RNA levels persistently <200 copies/mL, those with levels persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.[7,8] Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered virologic failure, and resistance testing should be attempted, particularly with HIV RNA >500 copies/mL. Management approaches should be the same as for patients with HIV RNA >1,000 copies/mL (as outlined below). When resistance testing cannot be performed because of low RNA levels, the decision of whether to empirically change ARVs should be made on a case-by-case basis, taking into account whether a new regimen expected to fully suppress viremia can be constructed.
- **HIV RNA ≥1,000 copies/mL and no current or previous drug resistance identified:** This scenario is almost always associated with suboptimal adherence. Conduct a thorough assessment 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:
  - Assess 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.
  - Address intolerance by symptomatic treatment (e.g., antiemetics, antidiarrheals), switch from one ARV in a regimen to another agent in the same drug class, or switch from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI) (see Adverse Effects).
  - Review food requirement for each medication, and assess whether the patient adheres to the requirement.
  - Assess if there is a recent history of gastrointestinal symptoms, such as vomiting or diarrhea, that may result in short-term malabsorption.
  - Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug Interactions and Tables 18a-18b for common interactions) and, if possible, make appropriate substitutions for ARV agents and/or concomitant medications.
  - Consider therapeutic drug monitoring if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected (see also Exposure-Response Relationship and Therapeutic Drug Monitoring).
  - Consider the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for more than 4 weeks before testing?). If the current regimen is well tolerated and there are no significant drug-drug or drug-food interactions, it is reasonable to continue the same regimen. If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen to an equally effective, more tolerable regimen. Two to four weeks

after treatment is resumed or started, repeat viral load testing; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain has emerged **(CIII)**.

- **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 in order to avoid progressive accumulation of resistance mutations.[40] In addition, several studies have shown that virologic responses to new and active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 cell counts at the time of regimen changes, thus the change is best done before worsening of viremia or decline in CD4 count.[9,41] The availability of newer ARVs, 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 present and are addressed in the clinical scenarios outlined below.

Managing Virologic Failure in Different Clinical Scenarios

See Table 10 for a summary of these recommendations.

Virologic Failure with First Antiretroviral Regimen

- **NNRTI plus NRTI regimen:** Patients with virologic failure while on an NNRTI-based regimen often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to lamivudine (3TC) and emtricitabine (FTC). Several studies have explored the efficacy of a pharmacokinetically boosted PI or an INSTI with at least one active NRTI, or of a boosted PI with an INSTI.[36,42-44] Two studies found that regimens containing a ritonavir-boosted PI (PI/r) combined with at least one active NRTI were as active as regimens containing the PI/r combined with RAL.[36,43,45] Two studies also demonstrated higher rates of virologic suppression with use of a PI/r plus at least one active NRTI than with a PI/r alone.[42,43] Although LPV/r was the PI used in these studies, it is likely that other pharmacokinetically boosted PIs would have similar activities, but this has not been demonstrated in large clinical trials. On the basis of these studies, even patients with NRTI resistance can often be treated with a pharmacokinetically boosted PI plus at least one active NRTI or RAL **(AIII)**. Although data are limited, the other INSTIs (i.e., EVG or DTG) combined with a pharmacokinetically boosted PI may also be options in this setting **(AIII)**. In an interim analysis comparing DTG versus LPV/r, both administered with two NRTIs in patients who experienced virologic failure while receiving a first-line NNRTI regimen, the DTG arm was superior to the LPV/r arm **(AIII)**.[44] Thus, an INSTI with two NRTIs is also an option after failure of first-line NNRTI-based therapy. If only one of the NRTIs is fully active or if adherence is a concern, DTG is preferred over EVG or RAL **(AIII)**.
- **Pharmacokinetically boosted PI plus NRTI regimen:** In this scenario, most patients will have either no resistance or resistance limited to 3TC and FTC.[46,47] Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. A systematic review of multiple randomized trials of PI/r first-line failure showed that maintaining the same regimen, with efforts to enhance adherence, is as effective as changing to new regimens with or without drugs from new classes **(AII)**.[48] If the regimen is well tolerated and there are no concerns regarding drug-drug or drug-food interactions or drug resistance, the regimen can be continued with adherence support and viral monitoring. Alternatively, if poor tolerability or drug interactions may be contributing to virologic failure, the regimen can be modified to include a different pharmacokinetically boosted PI plus either at least one active NRTI **(AIII)**, or an INSTI **(BIII)**. The regimen can also be switched to a new non-PI-based regimen that includes at least two fully active agents, such as an INSTI plus two NRTIs **(AIII)**. As noted above, if only one of the NRTIs is fully active or if adherence is a concern, DTG is preferred over EVG or RAL **(AIII)**.
- **INSTI plus NRTI regimen:** Virologic failure with a regimen consisting of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC/FTC and possibly the INSTI.[49] Viruses with EVG or RAL resistance often remain susceptible to DTG.[41] In contrast, in clinical trials, persons who experienced

virologic failure while receiving DTG plus two NRTIs as first-line therapy were unlikely to develop phenotypic resistance to DTG.[49] There are no clinical trial data to guide therapy for first-line INSTI failures, although one might extrapolate from the data for NNRTI-based failures. Thus, patients with first-line INSTI plus NRTIs failure without INSTI resistance should respond to a pharmacokinetically boosted PI plus two NRTIs (at least one active) **(AIII)**, a pharmacokinetically boosted PI plus an INSTI **(BII)**, or DTG plus two NRTIs (at least one active) **(AIII)**. If the virus is found to have resistance to RAL and EVG but remains susceptible to DTG, regimen options include a pharmacokinetically boosted PI plus two NRTIs (at least one active) **(AIII)**, twice-daily DTG plus two active NRTIs **(AIII)**, or twice-daily DTG plus a pharmacokinetically boosted PI **(AIII)**. If no resistance is identified, the patient should be managed as outlined above in the section on virologic failure without resistance.

Second-Line Regimen Failure and Beyond

- **Drug resistance with fully active ART options:** Depending on treatment history and drug-resistance data, one can predict whether or not to include a fully active pharmacokinetically boosted PI in future regimens. For example, those who have no documented PI resistance and previously have never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. In this setting, viral suppression should be achievable using a pharmacokinetically boosted PI combined with either two NRTIs or an INSTI—provided the virus is susceptible to these drugs. If a fully active pharmacokinetically boosted PI is not an option, the new regimen should include at least two, and preferably three, fully active agents. Drugs should be selected based on the likelihood that they will be 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 ART options:** Use of currently available ARVs has resulted in a dramatic decline in the number of patients who have few treatment options because of multiclass drug resistance.[50,51] Despite this progress, there remain patients who have experienced toxicities and/or developed resistance to all or most currently available drugs. If maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize increasing resistance which may compromise future regimens. Consensus on the optimal management of these patients is lacking. If resistance to NNRTIs, T20, DTG, EVG, or RAL are identified, there is rarely a reason to continue these drugs, as there is little evidence that keeping them on the regimen helps delay disease progression **(BII)**. Moreover, continuing these drugs, in particular INSTIs, may allow for increasing resistance and 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.[50,52] Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 cell count increases, reduces the risk of disease progression.[53] Other cohort studies suggest continued immunologic and clinical benefits with even modest reductions in HIV RNA levels.[54,55] However, these potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations. In general, adding a single fully active ARV 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 research studies or expanded access programs or may qualify for single-patient access to an investigational new drug as specified in Food and Drug Administration regulations: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm163982.htm. Information about two agents that are in late-stage clinical studies, ibalizumab and fostemsavir, can be found at https://aidsinfo.nih.gov/drugs/511/ibalizumab/0/professional and https://aidsinfo.nih.gov/drugs/508/fostemsavir/0/professional.
- **Previously treated patients with suspected drug resistance who present with limited information (i.e., incomplete or no self-reported history, medical records, or resistance-testing results):** Every effort should be made to obtain the patient's ARV history and prior drug-resistance testing 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 selection of the next regimen. Another strategy is to start two or three drugs predicted to be active on the basis of the patient's treatment history. If there is no available ARV history, a clinician may consider using agents with high barrier to resistance, such as DTG and/or boosted DRV, as part of the regimen. HIV RNA and resistance testing should be obtained approximately 2 to 4 weeks after re-initiation of therapy and patients should be closely monitored for virologic responses.

Table 10. Antiretroviral Options for Patients with Virologic Failure (page 1 of 2)

Designing a new regimen for patients with treatment failure should always be guided by results from current and past resistance testing and ARV history. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. It is also crucial to provide continuous adherence support to all patients before and after regimen changes. For more detailed descriptions, please refer to the text above and/or consult an expert in drug resistance to assist in the design of a new regimen.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[1,2]	Goal
First Regimen Failure	NNRTI + 2 NRTIs	Most likely resistant to NNRTI +/- 3TC/FTC (i.e., NNRTI mutations +/-M184V/I, without resistance to other NRTIs)[3]	• Boosted PI + 2 NRTIs (at least 1 active) **(AIII)**; or • INSTI + 2 NRTIs (if only 1 of the NRTIs is fully active, or if adherence is a concern, DTG is preferred over EVG or RAL) **(AIII)**; or • Boosted PI + INSTI **(AIII)**	Resuppression
	Boosted PI + 2 NRTIs	Most likely no resistance or resistance only to 3TC/FTC (i.e., M184V/I, without resistance to other NRTIs)[3]	• Continue same regimen **(AII)**; or • Another boosted PI + 2 NRTIs (at least 1 active) **(AII)**; or • INSTI + 2 NRTIs (at least 1 active) (if only 1 of the NRTIs is fully active, or if adherence is a concern, DTG is preferred over EVG or RAL) **(AIII)**; or • Boosted PI + INSTI **(BIII)**	Resuppression
	INSTI + 2 NRTIs	3TC/FTC (i.e., only M184V/I, without resistance to other NRTIs)[3] No INSTI resistance	• Boosted PI + 2 NRTIs (at least 1 active) **(AIII)**; or • DTG + 2 NRTIs (at least 1 active) **(AIII)**; or • Boosted PI + INSTI **(BIII)**	Resuppression
		EVG or RAL +/- 3TC/FTC (i.e., INSTI mutations +/- M184V/I, without resistance to other NRTIs)[3] Resistance to first-line DTG is rare	• Boosted PI + 2 NRTIs (at least 1 active) **(AIII)**; or • DTG[4] twice daily (if sensitive to DTG) + 2 active NRTIs **(AIII)**; or • DTG[4] twice daily (if sensitive to DTG) + a pharmacokinetically boosted PI **(AIII)**	Resuppression
Second Regimen Failure and Beyond	Drug resistance with active treatment options	Use past and current genotypic +/- phenotypic resistance testing and ART history in designing new regimen	• At least 2, and preferably 3, fully active agents **(AI)** • Partially active drugs may be used if no other options are available • Consider using ARV with a different mechanism of action	Resuppression

Table 10. Antiretroviral Options for Patients with Virologic Failure (page 2 of 2)

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[1,2]	Goal
Second Regimen Failure and Beyond, continued	Multiple or extensive drug resistance with few treatment options	Use past and current genotypic and phenotypic resistance testing to guide therapy Consider viral tropism assay if use of maraviroc is considered Consult an expert in drug resistance, if needed	• Identify as many active or partially active drugs as possible based on resistance testing results • Consider using ARV with a different mechanism of action • Consider enrollment into clinical trials or expanded access programs for investigational agents, if available • Discontinuation of ARVs **is not recommended**	Resuppression, if possible, otherwise, keep viral load as low as possible and CD4 cell count as high as possible
Previously Treated Patients with Suspected Drug Resistance, but Limited or Incomplete ART and Resistance History	Unknown	Obtain medical records if possible Resistance testing may be helpful in identifying prior drug resistance, even if the patient has been off ART, keeping in mind that resistance mutations may not be detected in the absence of drug pressure.	• Consider restarting the old regimen, and obtain viral load and resistance testing 2-4 weeks after reintroduction of therapy • If there is no available ARV history, consider initiating a regimen with drugs with high genetic barrier to resistance (e.g., DTG and/or boosted DRV)	Resuppression

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

[2] When switching an ARV regimen in a patient with HIV/HBV coinfection, ARV drugs active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.

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

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

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; 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

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 associated with breakthrough of HIV infection within the CNS compartment despite plasma HIV RNA suppression.[56-58] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging (MRI) and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis.[59] Measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most (though not all) patients, evidence of drug-resistant CSF virus. Drug-resistance testing of HIV in CSF can be used to guide changes in the treatment regimen according to principles outlined above for plasma HIV RNA resistance **(CIII)**. In these patients it may also be useful to consider CNS pharmacokinetics in drug selection in order to assure adequate concentrations of drugs within the CNS **(CIII)**. If CSF HIV 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)**.[60-63]

This "neurosymptomatic" CNS viral escape should be distinguished from: (1) incidental detection of asymptomatic mild CSF HIV RNA elevation that is usually transient with low levels of CSF HIV RNA, likely equivalent to plasma blips;[64,65] or (2) transient increase in CSF HIV RNA related to other CNS

infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster[66]). 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.[67] Unlike the "neurosymptomatic" CNS viral escape, these latter conditions do not currently warrant a change in ART.[68]

Summary

The management of treatment-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 cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug and food interactions, as well as review HIV RNA and CD4 cell 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 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 cell counts to delay clinical progression.

References

1. Kieffer TL, Finucane MM, Nettles RE, et al. Genotypic analysis of HIV-1 drug resistance at the limit of detection: virus production without evolution in treated adults with undetectable HIV loads. *J Infect Dis*. Apr 15 2004;189(8):1452-1465. Available at https://www.ncbi.nlm.nih.gov/pubmed/15073683.

2. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART. *JAMA*. Feb 16 2005;293(7):817-829. Available at https://www.ncbi.nlm.nih.gov/pubmed/15713771.

3. Lima V, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr*. May 1 2009;51(1):3-6. Available at https://www.ncbi.nlm.nih.gov/pubmed/19247185.

4. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis*. Jan 15 2009;48(2):260-262. Available at https://www.ncbi.nlm.nih.gov/pubmed/19113986.

5. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr*. Aug 1 2010;54(4):442-444. Available at https://www.ncbi.nlm.nih.gov/pubmed/20611035.

6. Ribaudo H, Lennox J, Currier J, al e. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. Presented at: 16th Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.

7. Antiretroviral Therapy Cohort C. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS*. Jan 28 2015;29(3):373-383. Available at http://www.ncbi.nlm.nih.gov/pubmed/25686685.

8. Boillat-Blanco N, Darling KE, Schoni-Affolter F, et al. Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. *Antivir Ther*. Jun 25 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24964403.

9. Eron JJ, Cooper DA, Steigbigel RT, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. *Lancet Infect Dis*. Jul 2013;13(7):587-596. Available at http://www.ncbi.nlm.nih.gov/pubmed/23664333.

10. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. Nov 2013;57(10):1489-1496. Available at http://www.ncbi.nlm.nih.gov/pubmed/23946221.

11. Taiwo B, Gallien S, Aga S, et al. HIV drug resistance evolution during persistent near-target viral suppression. Antiviral

Therapy 2010;15:A38.

12. Aleman S, Soderbarg K, Visco-Comandini U, Sitbon G, Sonnerborg A. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS*. May 3 2002;16(7):1039-1044. Available at https://www.ncbi.nlm.nih.gov/pubmed/11953470.

13. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. Apr 30 2004;18(7):981-989. Available at https://www.ncbi.nlm.nih.gov/pubmed/15096800.

14. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS*. Mar 31 2000;14(5):499-507. Available at https://www.ncbi.nlm.nih.gov/pubmed/10780712.

15. Mocroft A, Youle M, Moore A, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS*. Jan 26 2001;15(2):185-194. Available at https://www.ncbi.nlm.nih.gov/pubmed/11216926.

16. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. Mar 2010;201(5):662-671. Available at https://www.ncbi.nlm.nih.gov/pubmed/20102271.

17. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med*. Jul 24 2008;359(4):355-365. Available at https://www.ncbi.nlm.nih.gov/pubmed/18650513.

18. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med*. May 29 2003;348(22):2186-2195. Available at https://www.ncbi.nlm.nih.gov/pubmed/12773645.

19. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med*. May 29 2003;348(22):2175-2185. Available at https://www.ncbi.nlm.nih.gov/pubmed/12637625.

20. Reynes J, Arasteh K, Clotet B, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS*. Aug 2007;21(8):533-543. Available at https://www.ncbi.nlm.nih.gov/pubmed/17711378.

21. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet*. Apr 7 2007;369(9568):1169-1178. Available at https://www.ncbi.nlm.nih.gov/pubmed/17416261.

22. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. Jul 24 2008;359(4):339-354. Available at https://www.ncbi.nlm.nih.gov/pubmed/18650512.

23. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS*. Nov 13 2009;23(17):2289-2300. Available at https://www.ncbi.nlm.nih.gov/pubmed/19710593.

24. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. Oct 2 2008;359(14):1429-1441. Available at https://www.ncbi.nlm.nih.gov/pubmed/18832244.

25. Fatkenheuer G, Nelson M, Lazzarin A, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med*. Oct 2 2008;359(14):1442-1455. Available at https://www.ncbi.nlm.nih.gov/pubmed/18832245.

26. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. Aug 24 2013;382(9893):700-708. Available at http://www.ncbi.nlm.nih.gov/pubmed/23830355.

27. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med*. Feb 15 2001;344(7):472-480. Available at https://www.ncbi.nlm.nih.gov/pubmed/11172188.

28. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis*. Nov 1 2005;192(9):1537-1544. Available at https://www.ncbi.nlm.nih.

gov/pubmed/16206068.

29. Deeks SG, Lu J, Hoh R, et al. Interruption of enfuvirtide in HIV-1 infected adults with incomplete viral suppression on an enfuvirtide-based regimen. *J Infect Dis*. Feb 1 2007;195(3):387-391. Available at https://www.ncbi.nlm.nih.gov/pubmed/17205477.

30. Wirden M, Simon A, Schneider L, et al. Raltegravir has no residual antiviral activity in vivo against HIV-1 with resistance-associated mutations to this drug. *J Antimicrob Chemother*. Nov 2009;64(5):1087-1090. Available at https://www.ncbi.nlm.nih.gov/pubmed/19717396.

31. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med*. Aug 28 2003;349(9):837-846. Available at https://www.ncbi.nlm.nih.gov/pubmed/12944569.

32. Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet*. Aug 5 2006;368(9534):466-475. Available at https://www.ncbi.nlm.nih.gov/pubmed/16890833.

33. Molina JM, Lamarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis*. Jan 2012;12(1):27-35. Available at http://www.ncbi.nlm.nih.gov/pubmed/22015077.

34. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. Jul 2014;14(7):572-580. Available at http://www.ncbi.nlm.nih.gov/pubmed/24783988.

35. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. Nov 29 2014;384(9958):1942-1951. Available at http://www.ncbi.nlm.nih.gov/pubmed/25103176.

36. Second-Line Study Group, Boyd MA, Kumarasamy N, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet*. Jun 15 2013;381(9883):2091-2099. Available at http://www.ncbi.nlm.nih.gov/pubmed/23769235.

37. Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med*. Jul 17 2014;371(3):234-247. Available at http://www.ncbi.nlm.nih.gov/pubmed/25014688.

38. Prezista [package insert]. Food and Drug Administration. 2013. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021976s033_202895s010lbl.pdf. Accessed September 11, 2017.

39. Tivicay [package insert]. Food and Drug Administration. 2013. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf. Accessed February 11, 2017.

40. Hosseinipour MC, van Oosterhout JJ, Weigel R, et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS*. Jun 1 2009;23(9):1127-1134. Available at https://www.ncbi.nlm.nih.gov/pubmed/19417582.

41. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. *J Infect Dis*. Jan 19 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24446523.

42. Bunupuradah T, Chetchotisakd P, Ananworanich J, et al. A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study. *Antivir Ther*. 2012;17(7):1351-1361. Available at http://www.ncbi.nlm.nih.gov/pubmed/23075703.

43. Paton NI, Kityo C, Hoppe A. A pragmatic randomised controlled strategy trial of three second-line treatment options

for use in public health rollout programme settings: the Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial. 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013); 2013; Kuala Lumpur, Malaysia.

44. Aboud M, Kaplan R, Lombaard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. 9th IAS Conference on HIV Science; 2017; Paris, France.

45. La Rosa AM, Harrison LJ, Taiwo B, et al. Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. *Lancet HIV*. Jun 2016;3(6):e247-258. Available at https://www.ncbi.nlm.nih.gov/pubmed/27240787.

46. Lathouwers E, De Meyer S, Dierynck I, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther*. 2011;16(1):99-108. Available at https://www.ncbi.nlm.nih.gov/pubmed/21311113.

47. Stebbing J, Nathan B, Jones R, et al. Virological failure and subsequent resistance profiles in individuals exposed to atazanavir. *AIDS*. Aug 20 2007;21(13):1826-1828. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690587.

48. Zheng Y, Lambert C, Arendt V, Seguin-Devaux C. Virological and immunological outcomes of elvitegravir-based regimen in a treatment-naive HIV-2-infected patient. *AIDS*. Sep 24 2014;28(15):2329-2331. Available at http://www.ncbi.nlm.nih.gov/pubmed/25313590.

49. White KL, Raffi F, Miller MD. Resistance analyses of integrase strand transfer inhibitors within phase 3 clinical trials of treatment-naive patients. *Viruses*. Jul 2014;6(7):2858-2879. Available at http://www.ncbi.nlm.nih.gov/pubmed/25054884.

50. De Luca A, Dunn D, Zazzi M, et al. Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. *J Infect Dis*. Apr 15 2013;207(8):1216-1220. Available at http://www.ncbi.nlm.nih.gov/pubmed/23315324.

51. Paquet AC, Solberg OD, Napolitano LA, et al. A decade of HIV-1 drug resistance in the United States: trends and characteristics in a large protease/reverse transcriptase and co-receptor tropism database from 2003 to 2012. *Antivir Ther*. 2014;19(4):435-441. Available at http://www.ncbi.nlm.nih.gov/pubmed/24518099.

52. Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS*. May 7 1999;13(7):797-804. Available at https://www.ncbi.nlm.nih.gov/pubmed/10357378.

53. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. Dec 22 2000;14(18):2857-2867. Available at https://www.ncbi.nlm.nih.gov/pubmed/11153667.

54. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*. Jul 3-9 2004;364(9428):51-62. Available at https://www.ncbi.nlm.nih.gov/pubmed/15234856.

55. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr*. Sep 1 2004;37(1):1147-1154. Available at https://www.ncbi.nlm.nih.gov/pubmed/15319674.

56. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis*. Mar 1 2010;50(5):773-778. Available at https://www.ncbi.nlm.nih.gov/pubmed/20100092.

57. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *AIDS*. Sep 10 2012;26(14):1765-1774. Available at http://www.ncbi.nlm.nih.gov/pubmed/22614889.

58. Ferretti F, Gisslen M, Cinque P, Price RW. Cerebrospinal fluid HIV escape from antiretroviral therapy. *Curr HIV/AIDS Rep*. Jun 2015;12(2):280-288. Available at https://www.ncbi.nlm.nih.gov/pubmed/25860317.

59. Kugathasan R, Collier DA, Haddow LJ, et al. Diffuse white matter signal abnormalities on magnetic resonance imaging are associated with human immunodeficiency virus Type 1 viral escape in the central nervous system among patients

with neurological symptoms. *Clin Infect Dis*. Apr 15 2017;64(8):1059-1065. Available at https://www.ncbi.nlm.nih.gov/pubmed/28329096.

60. Letendre S. Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. *Top Antivir Med*. Nov 2011;19(4):137-142. Available at http://www.ncbi.nlm.nih.gov/pubmed/22156215.

61. Letendre SL, Mills AM, Tashima KT, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. *Clin Infect Dis*. Oct 2014;59(7):1032-1037. Available at http://www.ncbi.nlm.nih.gov/pubmed/24944232.

62. Calcagno A, Di Perri G, Bonora S. Pharmacokinetics and pharmacodynamics of antiretrovirals in the central nervous system. *Clin Pharmacokinet*. Oct 2014;53(10):891-906. Available at http://www.ncbi.nlm.nih.gov/pubmed/25200312.

63. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS*. Jan 28 2011;25(3):357-365. Available at https://www.ncbi.nlm.nih.gov/pubmed/21124201.

64. Eden A, Fuchs D, Hagberg L, et al. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis*. Dec 15 2010;202(12):1819-1825. Available at https://www.ncbi.nlm.nih.gov/pubmed/21050119.

65. Eden A, Nilsson S, Hagberg L, et al. Asymptomatic cerebrospinal fluid HIV-1 viral blips and viral escape during antiretroviral therapy: a longitudinal study. *J Infect Dis*. Dec 15 2016;214(12):1822-1825. Available at https://www.ncbi.nlm.nih.gov/pubmed/27683820.

66. Moling O, Rossi P, Rimenti G, Vedovelli C, Mian P. Varicella-zoster virus meningitis and cerebrospinal fluid HIV RNA. Scand *J Infect Dis*. 2001;33(5):398-399. Available at http://www.ncbi.nlm.nih.gov/pubmed/11440237.

67. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. Feb 2011;17(1):3-16. Available at http://www.ncbi.nlm.nih.gov/pubmed/21174240.

68. Ellis RJ, Letendre S, Vaida F, et al. Randomized trial of central nervous system-targeted antiretrovirals for HIV-associated neurocognitive disorder. *Clin Infect Dis*. Apr 2014;58(7):1015-1022. Available at http://www.ncbi.nlm.nih.gov/pubmed/24352352.

Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression (Last updated April 8, 2015; last reviewed April 8, 2015)

Panel's Recommendations

- Morbidity and mortality from several AIDS and non-AIDS conditions are increased in individuals with HIV despite antiretroviral therapy (ART)-mediated viral suppression, and are predicted by persistently low CD4 T lymphocyte (CD4) cell counts and/or persistent immune activation.
- ART intensification by adding antiretroviral (ARV) drugs to a suppressive ART regimen does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(AI)**.
- In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(BIII)**.
- No interventions designed to increase CD4 cell counts and/or decrease immune activation are recommended at this time (in particular, interleukin-2 **is not recommended [AI]**) because no intervention has been proven to decrease morbidity or mortality during ART-mediated viral suppression.
- Monitoring markers of immune activation and inflammation **is not recommended** because no immunologically targeted intervention has proven to improve the health of individuals with abnormally high biomarker levels, and many markers that predict morbidity and mortality fluctuate widely in individuals **(AII)**.
- Because there are no proven interventions to improve CD4 cell recovery and/or inflammation, efforts should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and exercise; treating hypertension and hyperlipidemia) **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

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 continues 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 II diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and frailty.[1] Although health-related behaviors and toxicities of antiretroviral (ARV) drugs may also contribute to the increased risk of illness and death, poor CD4 T lymphocyte (CD4) cell recovery, persistent immune activation, and inflammation likely also contribute to the risk.

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 to >500 cells/mm^3.[16]

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 (e.g., cancer chemotherapy, interferon, zidovudine,[17] or the combination of tenofovir disoproxil fumarate [TDF] and didanosine [ddI]).[18,19] If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., HCV, HIV-2) and serious medical conditions (e.g., malignancy) should also be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and/or in those with CD4 counts consistently below 100 cells/mm^3. In many cases, no obvious cause for suboptimal immunologic response can be identified.

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 ART 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)**. In individuals maintaining viral suppression, switching ARV drug classes in a suppressive regimen also does not consistently improve CD4 cell recovery and is not recommended **(BIII)**.[26] Two large clinical trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2, an immune-based therapy, in improving CD4 cell recovery. Interleukin-2 adjunctive therapy resulted in CD4 cell count increases but with no observable clinical benefit. Therefore, interleukin-2 **is not recommended (AI)**.[27] Other immune-based therapies that increase CD4 cell counts (e.g., growth hormone, interleukin-7) are under investigation. However, none of the therapies have been evaluated in clinical endpoint trials; therefore, whether any of these approaches will offer clinical benefit is unclear. Currently, such immune-based therapies should not be used except in the context of a clinical trial.

Persistent Immune Activation and Inflammation

Although poor CD4 cell recovery likely contributes to morbidity and mortality during ART-mediated viral suppression, there is increasing focus on persistent immune activation and inflammation as potentially independent mediators of risk. HIV infection results in heightened systemic immune activation and inflammation, effects that are evident during acute infection, persist throughout chronic untreated infection, and 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, 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] 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.[31,32] Even in individuals with CD4 counts >500 cells/mm^3, there is evidence that immune activation and inflammation contribute to morbidity and mortality.[33] Thus, innate immune activation and inflammation are potentially important targets for future interventions.

Although the drivers of persistent immune activation during ART are not completely understood, HIV persistence, coinfections, and microbial translocation likely play important roles.[28] Interventions to reduce each of these presumed drivers are currently being investigated. Importantly, adding ARV drugs to an already suppressive ART regimen (ART intensification) does not consistently improve immune activation.[20-23,25]

Although some studies have suggested that switching an ART regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation,[34,35] 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 commonly used medications with anti-inflammatory properties (e.g., statins, aspirin) are being studied, and preliminary evidence suggests that some may reduce immune activation in treated HIV infection.[36,37] However, because no intervention specifically targeting immune activation or inflammation has been studied in a clinical outcomes trial in treated HIV infection, no interventions to reduce immune activation are recommended at this time.

In the absence of proven interventions, there is currently no clear rationale to 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)**.

References

1. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med*. Feb 18 2011;62:141-155. Available at http://www.ncbi.nlm.nih.gov/pubmed/21090961.
2. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS*. Jul 27 2001;15(11):1369-1377. Available at https://www.ncbi.nlm.nih.gov/pubmed/11504958.
3. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis*. Mar 15 2009;48(6):787-794. Available at http://www.ncbi.nlm.nih.gov/pubmed/19193107.
4. Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. *AIDS*. Jul 31 2010;24(12):1867-1876. Available at http://www.ncbi.nlm.nih.gov/pubmed/20467286.
5. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. Feb 1 2007;44(3):441-446. Available at https://www.ncbi.nlm.nih.gov/pubmed/17205456.
6. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. Jan 17 2013;368(3):218-230. Available at http://www.ncbi.nlm.nih.gov/pubmed/23323898.
7. Engsig FN, Zangerle R, Katsarou O, et al. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery. *Clin Infect Dis*. May 2014;58(9):1312-1321. Available at http://www.ncbi.nlm.nih.gov/pubmed/24457342.
8. Lewden C, Bouteloup V, De Wit S, et al. All-cause mortality in treated HIV-infected adults with CD4 >=500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration{dagger}. *Int J Epidemiol*. Apr 2012;41(2):433-445. Available at http://www.ncbi.nlm.nih.gov/pubmed/22493325.
9. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. Apr 23 2008;22(7):841-848. Available at https://www.ncbi.nlm.nih.gov/pubmed/18427202.
10. Achhra AC, Amin J, Law MG, et al. Immunodeficiency and the risk of serious clinical endpoints in a well studied cohort of treated HIV-infected patients. *AIDS*. Jul 31 2010;24(12):1877-1886. Available at http://www.ncbi.nlm.nih.gov/pubmed/20588170.
11. Smurzynski M, Wu K, Benson CA, Bosch RJ, Collier AC, Koletar SL. Relationship between CD4+ T-cell counts/HIV-1 RNA plasma viral load and AIDS-defining events among persons followed in the ACTG longitudinal linked randomized trials study. *J Acquir Immune Defic Syndr*. Sep 1 2010;55(1):117-127. Available at https://www.ncbi.nlm.nih.gov/pubmed/20622677.

12. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. Aug 15 2010;51(4):435-447. Available at https://www.ncbi.nlm.nih.gov/pubmed/20597691.

13. Yong MK, Elliott JH, Woolley IJ, Hoy JF. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. *J Acquir Immune Defic Syndr*. Jul 1 2011;57(3):205-210. Available at http://www.ncbi.nlm.nih.gov/pubmed/21522014.

14. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. Aug 14-28 2006;166(15):1632-1641. Available at https://www.ncbi.nlm.nih.gov/pubmed/16908797.

15. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. Oct 18 2008;22(16):2143-2153. Available at https://www.ncbi.nlm.nih.gov/pubmed/18832878.

16. Young J, Psichogiou M, Meyer L, et al. CD4 cell count and the risk of AIDS or death in HIV-Infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. *PLoS Med*. 2012;9(3):e1001194. Available at http://www.ncbi.nlm.nih.gov/pubmed/22448150.

17. Huttner AC, Kaufmann GR, Battegay M, Weber R, Opravil M. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS*. May 11 2007;21(8):939-946. Available at https://www.ncbi.nlm.nih.gov/pubmed/17457087.

18. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS*. Mar 24 2005;19(6):569-575. Available at https://www.ncbi.nlm.nih.gov/pubmed/15802975.

19. Negredo E, Bonjoch A, Paredes R, Puig J, Clotet B. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis*. Sep 15 2005;41(6):901-905. Available at https://www.ncbi.nlm.nih.gov/pubmed/16107993.

20. Gandhi RT, Zheng L, Bosch RJ, et al. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. *PLoS Med*. 2010;7(8). Available at https://www.ncbi.nlm.nih.gov/pubmed/20711481.

21. Hatano H, Strain MC, Scherzer R, et al. Increase in 2-Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial. *J Infect Dis*. Nov 2013;208(9):1436-1442. Available at http://www.ncbi.nlm.nih.gov/pubmed/23975885.

22. Hunt PW, Shulman NS, Hayes TL, et al. The immunologic effects of maraviroc intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. *Blood*. Jun 6 2013;121(23):4635-4646. Available at http://www.ncbi.nlm.nih.gov/pubmed/23589670.

23. Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. *Proc Natl Acad Sci USA*. Jun 9 2009;106(23):9403-9408. Available at https://www.ncbi.nlm.nih.gov/pubmed/19470482.

24. Cuzin L, Trabelsi S, Delobel P, et al. Maraviroc intensification of stable antiviral therapy in HIV-1-infected patients with poor immune restoration: MARIMUNO-ANRS 145 study. *J Acquir Immune Defic Syndr*. Dec 15 2012;61(5):557-564. Available at http://www.ncbi.nlm.nih.gov/pubmed/22986949.

25. Buzon MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med*. Apr 2010;16(4):460-465. Available at https://www.ncbi.nlm.nih.gov/pubmed/20228817.

26. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS*. Jul 17 2010;24(11):1697-1707. Available at http://www.ncbi.nlm.nih.gov/pubmed/20467288.

27. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. Oct 15 2009;361(16):1548-1559. Available at https://www.ncbi.nlm.nih.gov/pubmed/19828532.

28. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. *Adv Immunol*. 2013;119:51-83. Available at http://www.ncbi.nlm.nih.gov/pubmed/23886064.

29. Lederman MM, Calabrese L, Funderburg NT, et al. Immunologic failure despite suppressive antiretroviral therapy is related to activation and turnover of memory CD4 cells. *J Infect Dis*. Oct 15 2011;204(8):1217-1226. Available at http://www.ncbi.nlm.nih.gov/pubmed/21917895.

30. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis*. May 15 2003;187(10):1534-1543. Available at https://www.ncbi.nlm.nih.gov/pubmed/12721933.

31. Hunt PW, Sinclair E, Rodriguez B, et al. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. *J Infect Dis*. Apr 21 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24755434.

32. Tenorio AR, Zheng Y, Bosch RJ, et al. Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non-AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment. *J Infect Dis*. May 1 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24795473.

33. Tien PC, Choi AI, Zolopa AR, et al. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. *J Acquir Immune Defic Syndr*. Nov 2010;55(3):316-322. Available at http://www.ncbi.nlm.nih.gov/pubmed/20581689.

34. Martinez E, D'Albuquerque PM, Llibre JM, et al. Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir. *AIDS*. Nov 28 2012;26(18):2315-2326. Available at http://www.ncbi.nlm.nih.gov/pubmed/23018438.

35. Lake JE, McComsey GA, Hulgan T, et al. Switch to raltegravir decreases soluble CD14 in virologically suppressed overweight women: the Women, Integrase and Fat Accumulation Trial. *HIV Med*. Aug 2014;15(7):431-441. Available at http://www.ncbi.nlm.nih.gov/pubmed/24506429.

36. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis*. Feb 2014;58(4):588-595. Available at http://www.ncbi.nlm.nih.gov/pubmed/24253250.

37. O'Brien M, Montenont E, Hu L, et al. Aspirin attenuates platelet activation and immune activation in HIV-infected subjects on antiretroviral therapy: A Pilot Study. *J Acquir Immune Defic Syndr*. Feb 12 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/23406976.

Regimen Switching in the Setting of Virologic Suppression (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommedations
• Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations.
• The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options **(AI)**.
• It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities, and cumulative resistance test results (if available) before selecting a new antiretroviral therapy (ART) regimen **(AI)**.
• Adverse events, the availability of ARVs with an improved safety profile, or the desire to simplify a regimen may prompt a regimen switch. Within-class and between-class switches can usually maintain viral suppression, provided that there is no viral resistance to the ARV agents in the new regimen **(AI)**.
• Monotherapy with either a boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) has been explored in several trials or cohort studies, and has been associated with an unacceptable rate of virologic failure and the development of resistance; therefore, monotherapy as a switching strategy **is not recommended (AII)**.
• When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs active against HBV infection should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.
• Consultation with an HIV specialist should be considered when planning a regimen switch for a patient with a history of resistance to one or more drug classes **(BIII)**.
• More intensive monitoring to assess tolerability, viral suppression, adherence, and laboratory changes is recommended during the first 3 months after a regimen switch **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
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 patients living with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in treatment and a better understanding of drug resistance make it possible to consider switching an effective regimen to another regimen in some situations (see below). When considering such a switch, clinicians must keep several key principles in mind to maintain viral suppression while addressing concerns with the current regimen.

Reasons to Consider Regimen Switching in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and dosing frequency
- To enhance tolerability and decrease short- or long-term toxicity (see Adverse Effects of Antiretroviral Agents and Table 15 for more in-depth discussion)
- To prevent or mitigate drug-drug interactions (see Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur (see Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Switching

The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options **(AI)**. If a regimen switch results in virologic failure with the emergence of new resistance

mutations, the patient may require more complex or expensive regimens.

The review of a patient's full antiretroviral (ARV) history—including virologic responses, past ARV-associated toxicities, and cumulative resistance test results (if available)—is warranted before any treatment switch **(AI)**. If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can assume that no new resistance mutation emerged while the patient was on the suppressive regimen.

Once selected, a resistance mutation is generally archived in the HIV reservoir and is likely to re-emerge under the appropriate selective drug pressure, even if not detected in the patient's most recent resistance test. If resistance data are not available, resistance may often be inferred from a patient's treatment history. For example, a patient who experienced virologic failure on a lamivudine (3TC)- or emtricitabine (FTC)-containing regimen in the past is likely to have the M184V substitution, even if it is not documented. For patients with documented failure on a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an elvitegravir (EVG)- or raltegravir (RAL)-containing regimen, resistance to these drugs can also be assumed because these drugs generally have a lower barrier to resistance. If there is uncertainty about prior resistance, it is generally not advisable to switch a suppressive ARV regimen unless the new regimen is likely to be as active against potential resistant virus as the suppressive regimen. Consulting an HIV specialist is recommended when contemplating a regimen switch for a patient with a history of resistance to one or more drug classes.

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs active against HBV infection should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.

A commercially available test amplifies viral DNA in whole blood samples to detect the presence of archived resistance mutations in patients with suppressed HIV RNA. Its value in clinical practice is still being evaluated (see Drug-Resistance Testing).

More intensive monitoring to assess tolerability, viral suppression, adherence, and laboratory changes is recommended during the first 3 months after a regimen switch (see below).

Specific Regimen Switching Considerations (also see Adverse Effects of Antiretroviral Agents)

As with ART-naive patients, the use of a three-drug combination regimen is generally recommended when switching patients with suppressed viral loads to a new regimen. However, there is growing evidence that certain two-drug regimens can maintain virologic suppression, as discussed below. Monotherapy with either a boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) has been explored in several trials or cohort studies, and has been associated with an unacceptable rate of virologic failure and the development of resistance; therefore, monotherapy as a switching strategy **is not recommended (AII)**.

Strategies with Good Supporting Evidence

Within-class switches prompted by adverse events or the availability of ARVs within the same class that offer a better safety profile, reduced dosing frequency, or lower pill burden usually maintain viral suppression, provided there is no drug resistance to the new ARV. Some examples of within-class switch strategies are switching from efavirenz (EFV) to rilpivirine (RPV),[1] from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF),[2] from RAL to elvitegravir/cobicistat (EVG/c)[3] or dolutegravir (DTG), from ritonavir-boosted protease inhibitors (PIs/r) to PIs coformulated with cobicistat (PIs/c), or from boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with abacavir [ABC]/3TC).[4-6]

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. Some examples of between-class switch strategies are replacing a boosted PI with RPV,[7] or replacing an NNRTI or a boosted PI with an INSTI[8,9] or maraviroc (MVC). However, such switches

should be avoided if there is any doubt about the activity of the other agents in the regimen. When switching to MVC, co-receptor usage in virologically suppressed patients can be determined from proviral DNA (see Co-receptor Tropism Assays) obtained from peripheral blood mononuclear cells.[10,11] This strategy was used successfully in a randomized trial that switched virologically suppressed individuals from a regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a boosted PI to two NRTIs plus MVC.[12]

Two-Drug Regimens

Boosted Protease Inhibitor plus Emtricitabine or Lamivudine

There is growing evidence that a boosted PI-based regimen plus 3TC (i.e., ATV/r plus 3TC,[13] DRV/r plus 3TC,[14] or LPV/r plus 3TC[15]) can maintain virologic suppression in ART-naive individuals without baseline resistance mutations[14,16] and in patients with sustained viral suppression.[14,15,17] A ritonavir-boosted PI plus 3TC may be a reasonable option when the use of TDF, TAF, or ABC is contraindicated or not desirable **(BI)**.

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for at least 1 year and no history of virologic failure.[18] Participants were randomized to stay on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV. Virologic suppression was maintained in 95 to 96% of the participants in both arms at 48 weeks. DTG plus RPV can be a reasonable option when the use of NRTIs is not desirable and when resistance to either DTG or RPV is not expected **(AI)**.

Strategies for Virologically Suppressed Patients with a History of Treatment Failure

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir

The combination of EVG/c/TAF/FTC plus darunavir (DRV) has been shown to be a potential simplification strategy in patients with complicated salvage regimens.[19] A randomized controlled trial enrolled 135 virologically suppressed patients who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Eligible participants could have up to three thymidine analog resistance mutations and/or K65R mutations, but no history of either Q151M or T69 insertion mutations. The patients were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their original regimen. At 24 weeks, 97% of the patients in the EVG/c/TAF/FTC plus DRV arm maintained virologic suppression. The pill burden was reduced from an average of five tablets per day to two tablets per day.

Strategies with Some Supporting Evidence

Other switching strategies in patients with viral suppression have some evidence to support their use. These strategies cannot yet be recommended under most circumstances, or at all, until further evidence is available. If used, patients should be closely monitored to assure viral suppression is maintained. Some of these strategies are listed below.

Boosted Darunavir plus Raltegravir

The efficacy of this combination in patients with lower viral load levels was established in ART-naive patients. At 96 weeks, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC, but was inferior in patients with low pre-treatment CD4 T lymphocyte counts (<200 cells/mm^3) and high viral loads (>100,000 copies/mL).[20] The efficacy of switching to DRV/r plus RAL in virologically suppressed patients with no resistance to either DRV or RAL has not been explored.

Dolutegravir plus Lamivudine or Emtricitabine

The Lamidol trial evaluated a regimen of DTG and 3TC as a maintenance strategy in virologically suppressed patients who have no evidence of NRTI, INSTI, or PI resistance.[21] At 24 weeks, 103 of the 104 participants remained virologically suppressed. In a small (20-patient), single-arm study of DTG plus 3TC for ART-naive patients, 90% of patients achieved and maintained viral suppression at 48 weeks.[22] However, there is currently insufficient evidence to support use of this regimen, given that Lamidol was a single-arm trial and

has reported only short-term outcomes.

Strategies Not Recommended

Boosted Protease Inhibitor Monotherapy

The strategy of switching virologically suppressed patients without PI resistance from one ART regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and 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.[17,23,24] Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy. In most studies, resumption of NRTIs in patients experiencing low-level viral rebound has led to re-suppression.[25-28]

On the basis of the results from these studies, PI/r monotherapy should generally be avoided **(BI)**. No clinical trials evaluating the use of coformulated cobicistat-boosted PIs as monotherapy or comparing available PI/r monotherapy regimens have been conducted.

Dolutegravir Monotherapy

The strategy of switching virologically suppressed patients to DTG monotherapy has been evaluated in uncontrolled trials[29] and in cohorts.[30] It is associated with an unacceptable risk of virological failure and subsequent development of resistance. This strategy cannot be recommended **(AII)**.

Boosted Atazanavir plus Raltegravir

In a randomized study, virologically suppressed patients 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 discontinuations than switching to ATV/r plus TDF/FTC.[31] A regimen consisting of ATV/r plus RAL cannot currently be recommended **(AI)**.

Maraviroc plus Boosted Protease Inhibitor or Raltegravir

In a randomized controlled trial, virologically suppressed patients who were on a combination of NRTI plus a boosted PI, and who had CCR5-tropic HIV detected by proviral DNA testing, were randomized to one of three arms:

1. Patients remained on the same regimen,
2. Patients were switched to a regimen consisting of two NRTIs plus MVC, or
3. Patients were switched to a regimen consisting of a boosted PI plus MVC.

The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuations than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC cannot be recommended **(AI)**.[32]

Maraviroc plus Raltegravir

In a nonrandomized pilot study, virologically suppressed patients were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in 5 out of 44 patients.[33] Based on these study results, a combination of MVC and RAL **is not recommended (AII)**.

Monitoring after Treatment Changes

After a treatment switch, patients should be evaluated more closely for several months (i.e., a clinic visit or phone 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). The purpose of more intensive monitoring is to assess medication tolerance and conduct targeted laboratory testing if the patient had pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormalities were present and/or were a reason for the ARV change, or if lipid abnormalities are 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).

References

1. Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV clinical trials*. 2013;14(5):216-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24144898.

2. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *The Lancet HIV*. 2016;3(4):e158-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27036991.

3. Mills A, Crofoot G, Ortiz R, et al. Switching from twice-daily raltegravir plus tenofovir disoproxil fumarate/emtricitabine to once-daily elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in virologically suppressed, HIV-1-infected subjects: 48 weeks data. *HIV clinical trials*. 2014;15(2):51-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24710918.

4. Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. *HIV clinical trials*. 2012;13(5):233-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23134624.

5. Ghosn J, Carosi G, Moreno S, et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. *Antivir Ther*. 2010;15(7):993-1002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21041914.

6. Wohl DA, Bhatti L, Small CB, et al. The ASSURE study: HIV-1 suppression is maintained with bone and renal biomarker improvement 48 weeks after ritonavir discontinuation and randomized switch to abacavir/lamivudine + atazanavir. *HIV Med*. 2016;17(2):106-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26176344.

7. Palella FJ, Jr., Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS*. 2014;28(3):335-344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24670520.

8. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis*. 2014;14(7):590-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24908550.

9. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis*. 2014;14(7):581-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24908551.

10. Vitiello P, Brudney D, MacCartney M, et al. Responses to switching to maraviroc-based antiretroviral therapy in treated patients with suppressed plasma HIV-1-RNA load. *Intervirology*. 2012;55(2):172-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22286889.

11. Bonjoch A, Pou C, Perez-Alvarez N, et al. Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial. *The Journal of antimicrobial chemotherapy*. 2013;68(6):1382-1387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23354282.

12. Pett SL, Amin J, Horban A, et al. Week 96 results of the randomized, multicentre Maraviroc Switch (MARCH) study. *HIV Med*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28703491.

13. Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2015;15(7):775-784. Available at: http://

www.ncbi.nlm.nih.gov/pubmed/26062881.

14. Pulido F, Ribera E, Lagarde M, et al. Dual therapy with darunavir and ritonavir plus lamivudine versus triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of HIV-1 viral suppression: randomised, open label, non-inferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis*. 2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29020293.

15. Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2015;15(7):785-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26062880.

16. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. 2014;14(7):572-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24783988.

17. Ciaffi L, Koulla-Shiro S, Sawadogo AB, et al. Boosted protease inhibitor monotherapy versus boosted protease inhibitor plus lamivudine dual therapy as second-line maintenance treatment for HIV-1-infected patients in sub-Saharan Africa (ANRS12 286/MOBIDIP): a multicentre, randomised, parallel, open-label, superiority trial. *The Lancet HIV*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28566227.

18. Llibre JM, Hung C-C, Brinson C, et al. Phase III SWORD 1 & 2: Switch to DTG+RPV maintains virologic suppression through 48 weeks. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017; Seattle, WA. Available at: http://www.croiconference.org/sessions/phase-iii-sword-12-switch-dtgrpv-maintains-virologic-suppression-through-48-wks.

19. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *Journal of acquired immune deficiency syndromes*. 2017;74(2):193-200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27753684.

20. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014;384(9958):1942-1951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25103176.

21. Joly V, Burdet C, Landman R, et al. Promising results of Dolutegravir + lamivudine maintenance in ANRS 167 LAMIDOL Trial. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017; Seattle, WA. Available at: http://www.croiconference.org/sessions/promising-results-dolutegravir-lamivudine-maintenance-anrs-167-lamidol-trial.

22. Cahn P, Rolon MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. *Journal of the International AIDS Society*. 2017;20(1):1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28537061.

23. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS*. 2009;23(3):279-291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114854.

24. Arribas JR, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. *HIV Med*. 2012;13(7):398-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22413874.

25. Guiguet M, Ghosn J, Duvivier C, et al. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS*. 2012;26(18):2345-2350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22695301.

26. Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. *Journal of acquired immune deficiency syndromes*. 2007;44(4):417-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17159658.

27. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*.

2010;24(15):2365-2374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20802297.

28. Vernazza P, Daneel S, Schiffer V, et al. The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial. *AIDS*. 2007;21(10):1309-1315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17545707.

29. Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV-1: a randomized clinical trial. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017; Seattle, WA. Available at: http://www.croiconference.org/sessions/dolutegravir-maintenance-monotherapy-hiv-1-randomized-clinical-trial.

30. Blanco JL, Oldenbuettel C, Thomas R, et al. Pathways of resistance in subjects failing dolutegravir monotherapy. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017; Seattle, WA. Available at: http://www.croiconference.org/sessions/pathways-resistance-subjects-failing-dolutegravir-monotherapy.

31. van Lunzen J, Pozniak A, Gatell JM, et al. Brief report: switch to ritonavir-boosted atazanavir plus raltegravir in virologically suppressed patients with HIV-1 infection: a randomized pilot study. *Journal of acquired immune deficiency syndromes*. 2016;71(5):538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26605505.

32. Pett SL, Amin J, Horban A, et al. Maraviroc, as a switch option, in HIV-1-infected individuals with stable, well-controlled HIV replication and R5-tropic virus on their first nucleoside/nucleotide reverse transcriptase inhibitor plus ritonavir-boosted protease inhibitor regimen: Week 48 results of the randomized, multicenter MARCH Study. *Clin Infect Dis*. 2016;63(1):122-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27048747.

33. Katlama C, Assoumou L, Valantin MA, et al. Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study. *The Journal of antimicrobial chemotherapy*. 2014;69(6):1648-1652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24535278.

Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents (Last updated April 8, 2015; last reviewed April 8, 2015)

Panel's Recommendations
• Therapeutic drug monitoring (TDM) for antiretroviral agents is not recommended for routine use in the management of patients with HIV **(BII)**. • TDM may be considered in selected clinical scenarios, as discussed in the text below.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***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*

Knowledge about the relationship between a drug's systemic exposure (or concentration) and responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding why patients may respond differently to the same drug and dose, and in designing strategies to optimize drug response and tolerability.

Therapeutic drug monitoring (TDM) is a strategy used to guide dosing of certain antiarrhythmics, anticonvulsants, antineoplastics, and antimicrobial agents by using measured drug concentrations to improve the likelihood of the 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.

Several antiretroviral (ARV) agents meet most of the characteristics of agents suitable for a TDM strategy.[1] Specifically, some ARVs have considerable interpatient variability in drug concentrations. Other ARVs have known drug concentrations associated with efficacy and/or toxicity. In the case of other drugs, data from small prospective studies have demonstrated that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.[2,3]

TDM for ARV agents, however, is not recommended for routine use in the management of adults and adolescents with HIV (BII). This recommendation is based on multiple factors that limit the routine use of TDM in patients with HIV. These limiting factors include lack of prospective studies that demonstrate routine use of TDM improves clinical outcomes, uncertain therapeutic thresholds for most ARV agents, great intra- and inter-patient variability in drug concentrations achieved, and a lack of commercial laboratories to perform real time quantitation of ARV concentrations.[2-5]

Scenarios for Consideration of Therapeutic Drug Monitoring

Although routine use of TDM is not recommended, in some scenarios, ARV concentration data may be useful in patient management. In these cases, assistance from a clinical pharmacologist or a clinical pharmacist to interpret the concentration data may be advisable. These scenarios include the following:

- Suspicion of clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- Changes in pathophysiologic states that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- Among pregnant women who have risk factors for virologic failure (e.g., those not achieving viral suppression during an earlier stage of pregnancy), physiologic changes may result in reduced drug exposure during the later stages of pregnancy and thus further increase the risk of virologic failure;
- Heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;

- Use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials;
- Concentration-dependent, drug-associated toxicities; and
- Failure to achieve expected virologic response in medication-adherent patients.

Resources for Therapeutic Drug Monitoring Target Concentrations

Most TDM-proposed target concentrations for ARVs focus on a minimum concentration (C_{min}) (i.e., the plasma concentration at the end of a dosing interval before the next ARV dose). A summary of population average ARV C_{min} can be found in a review on the role of ARV-related TDM.[2] Population average C_{min} for newer ARVs can be found in the Food and Drug Administration-approved product labels.

Guidelines for the collection of blood samples and other practical suggestions related to TDM can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.[4]

Challenges and Considerations in Using Drug Concentrations to Guide Therapy

There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV concentrations in a patient requires the following:

- Quantification of the concentration of the drug, usually in plasma or serum;
- Determination of the patient's pharmacokinetic characteristics;
- Integration of information on patient adherence;
- Interpretation of the drug concentrations; and
- Adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical information, including the patient's ARV history and adherence before the TDM result. In addition, as knowledge of associations between ARV concentrations and virologic response evolves, clinicians who use a TDM strategy for patient management should evaluate the most up-to-date information regarding the exposure-response relationship of the tested ARV agent.

References

1. Spector R, Park GD, Johnson GF, Vesell ES. Therapeutic drug monitoring. *Clin Pharmacol Ther*. 1988;43(4):345-353. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3281773.
2. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit*. 2011;33(3):265-274. Available at http://www.ncbi.nlm.nih.gov/pubmed/21566505.
3. Kredo T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. *Cochrane Database Syst Rev*. 2009(3):CD007268. Available at http://www.ncbi.nlm.nih.gov/pubmed/19588422.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses*. 2002;18(12):825-834. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12201904.
5. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS*. 2008;3(3):266-271. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19372977.

Discontinuation or Interruption of Antiretroviral Therapy (Last updated April 8, 2015; last reviewed April 8, 2015)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression.[1-5] Thus, planned interruptions of ART are not generally recommended. However, unplanned interruption of ART may occur under certain circumstances as discussed below.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or interrupted access to drugs. Stopping ART for a short time (i.e., less than 1 to 2 days) because of a medical/surgical procedure can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Short-Term Therapy Interruption

When a Patient Experiences a Severe or Life-Threatening Toxicity or Unexpected Inability to Take Oral Medications:

- All components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short-Term Therapy Interruption (Up to 2 Weeks)

When All Regimen Components Have Similar Half-Lives and Do Not Require Food for Proper Absorption:

- All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.

When All Regimen Components Have Similar Half-Lives and Require Food for Adequate Absorption, and the Patient Cannot Take Anything by Mouth for a Short Time:

- Temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.

When the Antiretroviral Regimen Contains Drugs with Different Half-Lives:

- Stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]), which may increase the risk of selection of NNRTI-resistant mutations. Some experts recommend stopping the NNRTI first and the other antiretroviral drugs 2 to 4 weeks later. Alternatively, the NNRTI may be replaced with a ritonavir- or cobicistat-boosted protease inhibitor (PI/r or PI/c) for 4 weeks. The optimal time sequence for staggered discontinuation of regimen components, or replacement of the NNRTI with a PI/r or PI/c, has not been determined.

Planned Long-Term Therapy Interruptions

Planned long-term therapy interruptions are **not recommended** outside of controlled clinical trials **(AI)**. Several research studies are evaluating approaches to a functional (virological control in the absence of therapy) or sterilizing (virus eradication) cure of HIV infection. Currently, the only way to reliably test the effectiveness of these strategies may be to interrupt ART and closely monitor viral rebound over time in the setting of a clinical trial.

If therapy must be discontinued, patients should be aware of and understand the risks of viral rebound, acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), development of drug resistance, and the need for

chemoprophylaxis against opportunistic infections as a result of CD4 decline. Patients should be counseled about the need for close clinical and laboratory monitoring during therapy interruptions.

References

1. Holkmann Olsen C, Mocroft A, Kirk O, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. *HIV Med*. 2007;8(2):96-104. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17352766.

2. Kousignian I, Abgrall S, Grabar S, et al. Maintaining antiretroviral therapy reduces the risk of AIDS-defining events in patients with uncontrolled viral replication and profound immunodeficiency. *Clin Infect Dis*. 2008;46(2):296-304. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171266.

3. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet*. 2006;367(9527):1981-1989. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16782488&itool=iconabstr&query_hl=147&itool=pubmed_docsum.

4. DART Trial Team DTT. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. *AIDS*. 2008;22(2):237-247. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18097226.

5. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.

Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early[a]) HIV Infection (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection **(AI)** including those with early[a] HIV-1 infection.
• Once initiated, the goal of ART is to suppress plasma HIV-1 RNA to undetectable levels **(AIII)**. Testing for plasma HIV-1 RNA levels, CD4 T lymphocyte counts, and toxicity monitoring should be performed as recommended for patients with chronic HIV-1 infection **(AII)**.
• Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**.
• ART can be initiated before drug resistance test results are available. Because resistance to pharmacokinetically enhanced protease inhibitors (PIs) emerges slowly and clinically significant transmitted resistance to PIs is uncommon, a boosted darunavir (DRV) and emtricitabine (FTC) plus either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) are recommended regimens in this setting **(AIII)**. For similar reasons, dolutegravir (DTG) and FTC plus either TDF or TAF are also reasonable options, although data regarding transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of DTG regimens in early HIV infection is more limited **(AIII)**.
• When results of drug resistance testing are available, the treatment regimen can be modified if warranted **(AII)**. In patients without transmitted drug resistant virus, therapy should be initiated with one of the combination regimens that is recommended for patients with chronic HIV-1 infection (see What to Start) **(AIII)**.
• Patients starting ART should be willing and able to commit to treatment and should understand the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may recommend that patients defer therapy because of clinical or psychosocial factors.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
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*

[a] Early infection represents either acute or recent infection.

Definitions: Acute HIV-1 infection, the phase of HIV-1 disease immediately after infection, is typically characterized by an initial burst of viremia; although anti-HIV-1 antibodies are undetectable, HIV-1 RNA or p24 antigen is present. Recent infection is generally considered the phase up to 6 months after infection during which detectable anti-HIV-1 antibodies develop. Throughout this section, the term "early HIV-1 infection" is used to refer to either acute or recent HIV-1 infection.

Although some patients with acute HIV-1 infection experience fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms,[1-6] a recent prospective study shows that most patients have nonspecific and relatively mild signs and symptoms.[7] Primary care clinicians may fail to recognize acute HIV-1 infection because its manifestations are often similar to those of many other viral infections, such as influenza and infectious mononucleosis. Acute infection can also be asymptomatic. Table 11 provides practitioners with guidance to recognize, diagnose, and manage acute HIV-1 infection.

Diagnosing Acute HIV Infection

Health care providers should maintain a high level of suspicion for acute HIV-1 infection in patients who have a suggestive clinical syndrome—especially in those who report recent high-risk behavior (see Table 11).[8] Patients may not always disclose high-risk behaviors or perceive that such behaviors put them at risk for HIV-1 acquisition. Thus, even in the absence of reported high-risk behaviors, practitioners should have a low threshold for considering a diagnosis of acute HIV-1 infection, especially in high prevalence (≥1%) areas. Current statistics on the HIV prevalence in different geographical areas in the United States can be found at these websites: AIDSVu (http://aidsvu.org/) and the Centers for Disease Control and Prevention (CDC)'s

AtlasPlus (https://www.cdc.gov/nchhstp/atlas/).

Acute HIV-1 infection is usually defined as detectable HIV-1 RNA or p24 antigen in serum or plasma in the setting of a negative or indeterminate HIV-1 antibody test result.[8,9] Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen (often referred to as "4th Generation" assays) are now approved by the Food and Drug Administration, and the most recent CDC testing algorithm recommends them as the preferred assays to use for HIV screening, including for possible acute HIV-1 infection. Specimens that are reactive on an initial antigen/antibody (Ag/Ab) assay should be tested with an immunoassay that differentiates HIV-1 from HIV-2 antibodies.[10] Specimens that are reactive on the initial assay and have either negative or indeterminate antibody differentiation test results should be tested for quantitative or qualitative HIV-1 RNA; an undetectable HIV-1 RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV-1 RNA in this setting indicates that acute HIV-1 infection is highly likely.[10] HIV-1 infection should be confirmed later by subsequent testing to document HIV antibody seroconversion.

Some health care facilities may still be following HIV testing algorithms that recommend initial testing with an assay that only tests for anti-HIV antibodies. In such settings, when acute HIV-1 infection is suspected in a patient with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV-1 RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV-1 RNA test result indicate that acute HIV-1 infection is highly likely. Providers should be aware that a low-positive quantitative HIV-1 RNA level (e.g., <10,000 copies/mL) may represent a false-positive result because HIV-1 RNA levels in acute infection are generally (but not always) very high (e.g., >100,000 copies/mL).[5-7] Therefore, when a low-positive quantitative HIV-1 RNA test result is obtained, the HIV-1 RNA test should be repeated using a different specimen from the same patient because repeated false-positive HIV-1 RNA tests are unlikely.[6] The diagnosis of HIV-1 infection should be confirmed by subsequent documentation of HIV antibody seroconversion (see Table 11).

Treating Early HIV-1 Infection

Clinical trial data regarding the treatment of early HIV-1 infection are limited. However, a number of studies suggest that individuals who are treated during early infection may experience potential immunologic and virologic benefits.[11-19] In addition, because early HIV-1 infection is often associated with high viral loads and increased infectiousness,[20] and ART use by individuals with HIV reduces transmission to uninfected sexual partners,[21] treatment during early HIV-1 infection is expected to substantially reduce the risk of HIV-1 transmission.

The START and TEMPRANO trials evaluated timing of initiation of antiretroviral therapy (see Initiation of Antiretroviral Therapy). Although neither trial collected specific information on patients with early infection, the strength of the two studies' overall results and the evidence from other studies described above strongly suggest that, whenever possible, patients should begin ART upon diagnosis of early infection.

Considerations When Treating Early HIV-1 Infection

As with chronic infection, patients with early HIV-1 infection must be willing and able to commit to treatment. On a case-by-case basis, providers may recommend that patients defer therapy for clinical or psychosocial reasons. If treatment during early infection is deferred, patients should be maintained in care and every effort should be made to initiate therapy as soon as they are ready. Patients should also be reminded regularly of the importance of using condoms consistently and correctly during sex. The consistent use of condoms will reduce a patient's risk of transmitting HIV infection and help them to avoid exposure to sexually transmitted infections (http://www.cdc.gov/condomeffectiveness/).

Treating Early HIV-1 Infection During Pregnancy

Because early HIV-1 infection, especially in the setting of high level viremia, is associated with a high risk of perinatal transmission, all pregnant women with HIV-1 infection should start combination ART as soon as possible to prevent perinatal transmission of HIV-1.[22]

Treatment Regimen for Early HIV-1 Infection

Prior to the widespread use of integrase strand transfer inhibitors (INSTIs), data from the United States and Europe demonstrated that transmitted virus may be resistant to at least one antiretroviral drug in up to 16% of patients.[23,24] In one study, 21% of isolates from patients with acute HIV-1 infection demonstrated resistance to at least one drug.[25] Therefore, before initiating ART in a person with early HIV-1 infection, a specimen for genotypic antiretroviral (ARV) drug resistance testing should be obtained and the results of the test used to help guide selection of an ARV regimen **(AII)**. However, treatment initiation itself should not be delayed pending resistance testing results. Once the resistance test results are available, the treatment regimen can be modified if warranted **(AII)**.

As in chronic infection, the goal of therapy during early HIV-1 infection is to suppress plasma HIV-1 RNA to undetectable levels **(AIII)**. ART should be initiated with one of the combination regimens recommended for patients with chronic infection **(AIII)** (see What to Start). If available, the results of ARV drug resistance testing or the ARV resistance pattern of the source person's virus should be used to guide selection of the ARV regimen. Since therapy for early HIV infection is often started before the results of drug resistance testing are available, a pharmacologically boosted protease inhibitor (PI)-based regimen may be an appropriate choice (e.g., boosted darunavir [DRV]) because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon **(AIII)**. For similar reasons, dolutegravir (DTG) plus emtricitabine (FTC) and either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) are also reasonable treatment options, although data regarding transmission of INSTI-resistant HIV and the efficacy of DTG plus TDF/FTC in patients with acute/early infection are more limited **(AIII)**. DTG/abacavir (ABC)/lamivudine (3TC) is not recommended for empiric treatment of acute infection unless the patient is known to be HLA-B* 5701 negative, information that is seldom available when patients with acute infection present for care.

Given the increasing use of TDF/FTC as pre-exposure prophylaxis (PrEP) in HIV-negative individuals,[26-28] early infection may be diagnosed in some patients while they are taking TDF/FTC for PrEP. In this setting, resistance testing should be performed; however, as described above, use of a pharmacologically boosted PI (e.g., boosted DRV) and FTC plus either TDF or TAF—or DTG and FTC plus either TDF or TAF remain reasonable treatment options pending resistance testing results (see What to Start).

Patient Follow-Up

Testing for plasma HIV-1 RNA levels, CD4 cell counts, and toxicity monitoring should be performed as described in Laboratory Testing for Initial Assessment and Monitoring (e.g., HIV-1 RNA at initiation of therapy, after 2 to 8 weeks, then every 4 to 8 weeks until viral suppression, and thereafter, every 3 to 4 months) **(AII)**.

Duration of Therapy for Early HIV-1 Infection

Once ART is initiated in patients with early HIV infection, therapy should be continued indefinitely as in guidelines for patients with chronic infection. A large randomized controlled trial of patients with chronic HIV-1 infection found that treatment interruption was harmful in terms of increased risk of AIDS and non-AIDS events,[29] and that the strategy was associated with increased markers of inflammation, immune activation, and coagulation.[30] For these reasons and the potential benefit of ART in reducing the risk of HIV-1 transmission, the Panel recommends indefinite continuation of ART in patients treated for early HIV-1 infection **(AIII)**.

Table 11. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

Suspicion of Acute HIV-1 Infection:

- Acute HIV-1 infection should be considered in individuals with signs or symptoms described below and recent (within 2 to 6 weeks) high risk of exposure to HIV-1.[a]
- Signs, symptoms, or laboratory findings of acute HIV-1 infection may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
- High-risk exposures include sexual contact with a person who has HIV-1 infection or a person at risk of HIV-1 infection, sharing of injection drug use paraphernalia, or any exposure in which an individual's mucous membranes or breaks in the skin come in contact with bodily fluid potentially infected with HIV.
- **Differential diagnosis:** The differential diagnosis of HIV-1 infection may include but is not limited to viral illnesses such as Epstein-Barr virus (EBV) and non-EBV (e.g., cytomegalovirus) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis.

Evaluation/Diagnosis of Acute HIV-1 Infection:

- Acute HIV-1 infection is defined as detectable HIV-1 RNA or p24 antigen (the antigen used in currently available HIV antigen/antibody [Ag/Ab] combination assays) in the setting of a negative or indeterminate HIV-1 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-1 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV-1 infection is suspected requires plasma HIV-1 RNA testing to diagnose acute HIV-1 infection.
- A positive result on a quantitative or qualitative plasma HIV-1 RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV-1 infection is highly likely, in which case, the diagnosis of HIV-1 infection should be later confirmed by subsequent documentation of HIV antibody seroconversion.

Antiretroviral Therapy After Diagnosis of Early HIV-1 Infection:

- ART is recommended for all individuals with HIV **(AI)**, and should be offered to all patients with early HIV-1 infection.
- All pregnant women with early HIV-1 infection should begin ART as soon as possible for their health and to prevent perinatal transmission of HIV-1 **(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 the initiation of ART should be done as soon as possible, often prior to availability of resistance test results. If resistance is subsequently identified, treatment should be modified appropriately.
- If no resistance data are available, then a pharmacologically boosted PI-based regimen is recommended because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. Boosted DRV (DRV/r or DRV/c) plus FTC and either TDF or TAF is a recommended regimen in this setting **(AIII)**. For similar reasons, DTG plus FTC and either TDF or TAF are reasonable options although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited **(AIII)**.
- In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens recommended for patients with chronic HIV-1 infection (see What to Start) **(AIII)**.

[a] In some settings, behaviors that increase the risk of HIV-1 infection may not be recognized or perceived as risky by the health care provider or the patient, or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.

Key to Acronyms: ART = antiretroviral therapy; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. *AIDS*. Jan 1991;5(1):1-14. Available at https://www.ncbi.nlm.nih.gov/pubmed/1812848.
2. Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis*. Dec 1993;168(6):1490-1501. Available at https://www.ncbi.nlm.nih.gov/pubmed/8245534.
3. Kinloch-de Loes S, de Saussure P, Saurat JH, Stalder H, Hirschel B, Perrin LH. Symptomatic primary infection due to human immunodeficiency virus type 1: review of 31 cases. *Clin Infect Dis*. Jul 1993;17(1):59-65. Available at https://www.ncbi.nlm.nih.gov/pubmed/8353247.
4. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. Aug 15 1996;125(4):257-264. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8678387.
5. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med*. Jan 2 2001;134(1):25-29. Available at https://www.ncbi.nlm.nih.gov/pubmed/11187417.
6. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS*. May 24 2002;16(8):1119-1129. Available at https://www.ncbi.nlm.nih.gov/pubmed/12004270.
7. Robb ML, Eller LA, Kibuuka H, et al. Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand. *N Engl J Med*. Jun 02 2016;374(22):2120-2130. Available at https://www.ncbi.nlm.nih.gov/pubmed/27192360.
8. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. Sep 22 2006;55(RR-14):1-17. Available at https://www.ncbi.nlm.nih.gov/pubmed/16988643.
9. Pilcher CD, Christopoulos KA, Golden M. Public health rationale for rapid nucleic acid or p24 antigen tests for HIV. *J Infect Dis*. Apr 15 2010;201 Suppl 1:S7-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/20225950.
10. Centers for Disease Control and Prevention, Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. 2014. Available at https://stacks.cdc.gov/view/cdc/23447.
11. Hogan CM, Degruttola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. *J Infect Dis*. Jan 1 2012;205(1):87-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/22180621.
12. Grijsen ML, Steingrover R, Wit FW, et al. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized Primo-SHM trial. *PLoS Med*. 2012;9(3):e1001196. Available at http://www.ncbi.nlm.nih.gov/pubmed/22479156.
13. Hamlyn E, Ewings FM, Porter K, et al. Plasma HIV viral rebound following protocol-indicated cessation of ART commenced in primary and chronic HIV infection. *PLoS One*. 2012;7(8):e43754. Available at http://www.ncbi.nlm.nih.gov/pubmed/22952756.
14. Strain MC, Little SJ, Daar ES, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. *J Infect Dis*. May 1 2005;191(9):1410-1418. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809898.
15. SPARTAC Trial Investigators, Fidler S, Porter K, et al. Short-course antiretroviral therapy in primary HIV infection. *N Engl J Med*. Jan 17 2013;368(3):207-217. Available at http://www.ncbi.nlm.nih.gov/pubmed/23323897.
16. Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature*. Sep 28 2000;407(6803):523-526. Available at http://www.ncbi.nlm.nih.gov/pubmed/11029005.
17. Schuetz A, Deleage C, Sereti I, et al. Initiation of ART during early acute HIV infection preserves mucosal Th17 function and reverses HIV-related immune activation. *PLoS Pathog*. Dec 2014;10(12):e1004543. Available at http://www.ncbi.nlm.nih.gov/pubmed/25503054.
18. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med*. Sep 20 2004;200(6):761-770. Available at https://www.ncbi.nlm.nih.gov/pubmed/15365095.
19. Guadalupe M, Reay E, Sankaran S, et al. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol*. Nov 2003;77(21):11708-11717. Available at https://www.ncbi.nlm.nih.gov/pubmed/14557656.

20. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis*. May 1 2005;191(9):1403-1409. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809897.
21. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at https://www.ncbi.nlm.nih.gov/pubmed/21767103.
22. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2016. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
23. Kim D, Ziebell R, Saduvala N, et al. Trend in transmitted HIV-1 ARV drug resistance-associated mutations: 10 HIV surveillance areas, U.S., 2007–2010. Presented at: 20th Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, GA.
24. Hofstra LM, Sauvageot N, Albert J, et al. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. *Clin Infect Dis*. Nov 29 2015;62(5):655-663. Available at http://www.ncbi.nlm.nih.gov/pubmed/26620652.
25. Yanik EL, Napravnik S, Hurt CB, et al. Prevalence of transmitted antiretroviral drug resistance differs between acutely and chronically HIV-infected patients. *J Acquir Immune Defic Syndr*. Oct 1 2012;61(2):258-262. Available at http://www.ncbi.nlm.nih.gov/pubmed/22692092.
26. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. Dec 30 2010;363(27):2587-2599. Available at http://www.ncbi.nlm.nih.gov/pubmed/21091279.
27. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. Aug 2 2012;367(5):399-410. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784037.
28. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. Aug 2 2012;367(5):423-434. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784038.
29. Strategies for Management of Antiretroviral Therapy Study G, El-Sadr WM, Lundgren J, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. Nov 30 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/pubmed/17135583.
30. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. Oct 21 2008;5(10):e203. Available at https://www.ncbi.nlm.nih.gov/pubmed/18942885.

Adolescents and Young Adults with HIV (Last updated January 28, 2016; last reviewed January 28, 2016)

Key Summary and Panel's Recommendations
• Adolescents living with HIV largely belong to two distinct groups—those who acquired HIV in infancy, and are heavily antiretroviral therapy (ART)-experienced, and those who acquired HIV more recently during their teens. • ART is recommended for all individuals with HIV **(AI)** to reduce morbidity and mortality. Thus, ART is also recommended for ART-naive adolescents. However, before initiation of therapy, adolescents' readiness and ability to adhere to therapy within their psychosocial context need to be carefully considered as part of therapeutic decision making **(AIII)**. • Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the success in achieving sustained viral suppression **(AII)**. • The adolescent sexual maturity rating can be helpful to guide regimen selection for initiation of or changes in ART as recommended by either these Adult and Adolescent ARV Guidelines or the Pediatric ARV Guidelines. These Adult/Adolescent Guidelines are more appropriate for postpubertal adolescents (i.e., sexual maturity rating IV or V) **(AIII)**. • Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings. Adult providers should be sensitive to the challenges associated with such transitions, consulting and collaborating with adolescent HIV care providers to insure adolescents' successful transition and continued engagement in care **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
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*

Older children and adolescents now make up the largest percentage of children with HIV cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 26% of the approximately 50,000 newly diagnosed with HIV in 2010 were among youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% among young men who have sex with men (MSM).[1] Among youth living with HIV in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they had HIV.[2] Trends in HIV/AIDS prevalence indicate that the disproportionate burden of HIV among racial minorities is even greater among minority youth 13 to 24 years of age than among those older than 24 years.[3] Furthermore, trends for all HIV diagnoses among adolescents and young adults in 46 states and 5 U.S. dependent areas from 2007 to 2010 decreased or remained stable for all transmission categories except among young MSM. Adolescents with HIV represent a heterogeneous group in terms of socio-demographics, mode of HIV acquisition, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications to use.

Most adolescents who acquire HIV do so through sex. Many of them are recently infected and unaware of their HIV status. Thus, many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage to and engagement in care, and initiation of ART.[4] High grade viremia was reported in a cohort of youth living with HIV identified by adolescent HIV specialty clinics in 15 major metropolitan U.S. cities. The mean HIV viral load for the cohort was 94,398 copies/ml; 30% of the youth were not successfully linked to care.[5] A study among adolescents with HIV and young adults presenting for care identified primary genotypic resistance mutations to ARV medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing.[6] In an ARV treatment trial, a cohort of treatment-naive youth who had behaviorally acquired HIV showed substantial multiclass resistance.[7] As these youth were naive to all ART, this reflects transmission of resistant virus. This transmission dynamic reflects that a substantial proportion of youth's sexual partners are likely older and

may be more ART-experienced; thus, using baseline resistance testing to guide initial therapy in youth who have recently acquired HIV and are naive to ART is imperative.

A limited but increasing number of adolescents with HIV are long-term survivors of HIV acquired perinatally or in infancy through blood products. These adolescents are usually heavily ART-experienced and may have a unique clinical course that differs from that of adolescents who acquire HIV later in life.[8] Adolescents who acquired HIV perinatally or in infancy were often started on ART early in life with mono- or dual-therapy regimens resulting in incomplete viral suppression and emergence of viral resistance. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be selected on the basis of the same guiding principles used for heavily ART-experienced adults (see Virologic Failure section).

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and compete with their concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and need to fit in with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage and retain adolescents in care so they can improve and maintain their health for the long term. Given challenges with youth remaining in care and achieving long-term viral suppression,[9] additional considerations may be given to more intensive case management approaches.[10,11] Adolescents may seek care in several settings including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics.[12] Where youth services are available, they may be helpful to consider as one approach to enhancing HIV care engagement and retention among adolescents.[13] Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.[12,14]

Antiretroviral Therapy Considerations in Adolescents

The results from the START and TEMPRANO trials that favor initiating ART in all individuals who are able and willing to commit to treatment, and can understand the benefits and risks of therapy and the importance of excellent adherence, are discussed elsewhere in these guidelines (see Initiation of Antiretroviral Therapy). Neither of these trials included adolescents; however, recommendations based on these trials have been extrapolated to adolescents based on the expectation that they will derive benefits from early ART similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of American youth with HIV, their ability to adhere to therapy needs to be carefully considered as part of therapeutic decision making concerning the risks and benefits of starting treatment. Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the success in achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR) (also known as Tanner stage) can be helpful when ART initiation is being considered for this population (see SMR table). Adult guidelines for ART initiation or regimen changes (see What to Start) are usually appropriate for postpubertal adolescents (SMR IV or V) because the clinical course of HIV infection in postpubertal adolescents who acquired HIV sexually or through injection drug use during adolescence is more similar to that in adults than that in children. Adult guidelines can also be useful for postpubertal youth who acquired HIV perinatally and whose long-term HIV infection has not affected their sexual maturity (SMR IV or V). Pediatric guidelines for ART may be more appropriate for adolescents who acquired HIV during their teen years (e.g., through sex), but who are sexually immature (SMR III or less) and for adolescents who acquired HIV perinatally with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other comorbidities (SMR III or less) (see What to Start in the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection). Postpubertal youth who acquired HIV perinatally often have treatment challenges associated with the long-term use of ART that mirror those of ART-experienced adults, such as extensive resistance, complex

regimens, and adverse drug effects (see also Virologic Failure, Poor CD4 Recovery, Regimen Switching in the Setting of Virologic Suppression, and Adverse Effects of Antiretroviral Agents). Postpubertal adolescents who acquired HIV perinatally may also have comorbid cognitive impairments that compound adherence challenges common among youth.[15]

Dosage of ARV drugs should be prescribed according to the SMR and not solely on the basis of age.[16,17] Adolescents in early puberty (i.e., SMR I-III) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., SMR IV-V) should follow adult dosing schedules. However, SMR stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in children with perinatally acquired HIV,[18] continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each ARV medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition youth from pediatric to adult doses. Youth who are in their growth spurt period (i.e., SMR III in females and SMR IV in males) following adult or pediatric dosing guidelines and adolescents who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in each of these selected circumstances to help guide therapy decisions. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.[19]

Adherence Concerns in Adolescents

Adolescents with HIV are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of adolescents with HIV, who frequently lack both health insurance and experience with health care systems. Studies in adolescents who acquired HIV during their teen years and in adolescents with perinatal acquisition demonstrate that many adolescents in both groups face numerous barriers to adherence.[20-22] Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.[23] Reasons that adolescents with HIV often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV diagnosis;
- Misinformation;
- Distrust of the medical establishment;
- Fear of ART and lack of confidence in the effectiveness of medications;
- Low self-esteem;
- Unstructured and chaotic lifestyles;
- Mood disorders and other mental illness;
- Lack of familial and social support;
- Lack of or inconsistent access to care or health insurance; and
- Risk of inadvertent disclosure of their HIV status if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, beepers, timers, and pill boxes) that are stylish and/or inconspicuous.[24] In a randomized controlled study among nonadherent youth 15 to 24 years of age, youth who received cell phone medication reminders demonstrated significantly better adherence

and lower viral loads than youth who did not receive the reminder calls.[25] It is important to make medication adherence user-friendly and to avoid stigmatizing as much as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers.[26-28] Directly observed therapy may be considered for some adolescents with HIV such as those with mental illness.[29-33]

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere to therapy needs to be considered as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for adolescents with HIV frequently manage youth who, although needing therapy, pose significant concerns regarding their ability to adhere to therapy. In these cases, the following strategies can be considered:

1. A short-term deferral of treatment until adherence is more likely or while adherence-related problems are aggressively addressed;
2. An adherence testing period in which a placebo (e.g., vitamin pill) is administered; and
3. The avoidance of any regimens with low genetic resistance barriers.

Such decisions are ideally individualized to each patient and should be made carefully in context with the individual's clinical status. For a more detailed discussion on specific therapy and adherence issues for adolescents with HIV, see the Adherence to the Continuum of Care section of these guidelines and the Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection.[19]

Special Considerations in Adolescents

All adolescents should be screened for sexually transmitted diseases (STDs), in particular human papilloma virus (HPV). In young MSM, screening for STDs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population.[34] For a more detailed discussion on STDs, see the most recent CDC guidelines[35] and the adult and pediatric opportunistic infection treatment and prevention guidelines on HPV among adolescents with HIV.[36,37] Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for female adolescents with HIV is especially important. Contraception, including the interaction of specific ARV drugs with hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see Women with HIV and the Perinatal Guidelines.[38] Finally, transgender youth with HIV represent an important population that requires additional psychosocial and healthcare considerations. For a more detailed discussion, see Adolescent Trials Network (ATN) Transgender Youth Resources.

Transitioning Care

Given lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for children, adolescents, and young adults with HIV. A successful transition requires an awareness of some 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. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as medical insurance; the adolescent's degree of independence/autonomy and decisional capacity; patient confidentiality; and informed consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients. As an additional complication to this transition, adolescents with HIV belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial considerations and needs:

- Adolescents who acquired HIV perinatally—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for ART; and higher mortality risk—and
- Youth who more recently acquired HIV during their adolescence—who would likely be in earlier stages of HIV infection and have higher CD4 cell counts; these adolescents would be less likely to have viral drug resistance and may benefit from simpler treatment regimen options.

To maximize the likelihood of a successful transition, interventions to facilitate transition are best implemented early on.[39] These interventions include the following:

- Developing an individualized transition plan to address comprehensive care needs including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between adolescent and adult clinics;
- Identifying adult care providers willing to care for adolescents and young adults;
- Addressing 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;
- Helping youth develop life skills, including counseling them on the appropriate use of a primary care provider and how to manage appointments, the importance of prompt symptom recognition and reporting, and the importance of self-efficacy in managing medications, insurance, and assistance benefits;
- Identifying an optimal clinic model based on specific needs (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
- Implementing ongoing evaluation to measure the success of a selected model;
- Engaging adult and adolescent care providers in regular multidisciplinary case conferences;
- Implementing interventions that may improve outcomes, such as support groups and mental health consultation;
- Incorporating a family planning component into clinical care; and
- Educating HIV care teams and staff about transitioning.

Discussions regarding transition should begin early and before the actual transition process.[40] Attention to the key interventions noted above will likely improve adherence to appointments and avert the potential for a youth to fall through the cracks, as it is commonly referred to in adolescent medicine. For a more detailed discussion on specific topics on transitioning care for adolescents and young adults, see HIV Clinical Resource's Transition to Adult Care Guideline.

References

1. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2010. HIV Surveillance Supplemental Report 2012;17(No. 3, part A). Table 5a. 2012. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed January 6, 2015.
2. Centers for Disease C, Prevention. Vital signs: HIV infection, testing, and risk behaviors among youths—United States. *MMWR Morb Mortal Wkly Rep*. Nov 30 2012;61(47):971-976. Available at http://www.ncbi.nlm.nih.gov/pubmed/23190571.
3. Centers for Disease Control and Prevention. HIV Surveillance in Adolescents and Young Adults. Available at http://www.cdc.gov/hiv/pdf/statistics_surveillance_Adolescents.pdf. Accessed January 15, 2016.
4. Philbin MM, Tanner AE, Duval A, Ellen J, Kapogiannis B, Fortenberry JD. Linking HIV-positive adolescents to care in 15 different clinics across the United States: Creating solutions to address structural barriers for linkage to care. *AIDS Care*. Jan 2014;26(1):12-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/23777542.
5. Ellen JM, Kapogiannis B, Fortenberry JD, et al. HIV viral load levels and CD4+ cell counts of youth in 14 cities. *AIDS*. May 15 2014;28(8):1213-1219. Available at http://www.ncbi.nlm.nih.gov/pubmed/25028912.
6. Viani RM, Peralta L, Aldrovandi G, et al. Prevalence of primary HIV-1 drug resistance among recently infected adolescents: a multicenter adolescent medicine trials network for HIV/AIDS interventions study. *J Infect Dis*. Dec 1 2006;194(11):1505-1509. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17083034.
7. Agwu AL, Bethel J, Hightow-Weidman LB, et al. Substantial multiclass transmitted drug resistance and drug-relevant polymorphisms among treatment-naive behaviorally HIV-infected youth. *AIDS Patient Care STDS*. Apr 2012;26(4):193-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/22563607.
8. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr*. Jun 1 2011;57(2):165-173. Available at http://www.ncbi.nlm.nih.gov/pubmed/21407086.
9. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. *AIDS Patient Care STDS*. Mar 2014;28(3):128-135. Available at http://www.ncbi.nlm.nih.gov/pubmed/24601734.
10. Hightow-Weidman LB, Smith JC, Valera E, Matthews DD, Lyons P. Keeping them in "STYLE": finding, linking, and retaining young HIV-positive black and Latino men who have sex with men in care. *AIDS Patient Care STDS*. Jan 2011;25(1):37-45. Available at http://www.ncbi.nlm.nih.gov/pubmed/21162690.
11. Sitapati AM, Limneos J, Bonet-Vazquez M, Mar-Tang M, Qin H, Mathews WC. Retention: building a patient-centered medical home in HIV primary care through PUFF (Patients Unable to Follow-up Found). *J Health Care Poor Underserved*. Aug 2012;23(3 Suppl):81-95. Available at http://www.ncbi.nlm.nih.gov/pubmed/22864489.
12. Tanner AE, Philbin MM, Duval A, et al. "Youth friendly" clinics: Considerations for linking and engaging HIV-infected adolescents into care. *AIDS Care*. Feb 2014;26(2):199-205. Available at http://www.ncbi.nlm.nih.gov/pubmed/23782040.
13. Davila JA, Miertschin N, Sansgiry S, Schwarzwald H, Henley C, Giordano TP. Centralization of HIV services in HIV-positive African-American and Hispanic youth improves retention in care. *AIDS Care*. 2013;25(2):202-206. Available at http://www.ncbi.nlm.nih.gov/pubmed/22708510.
14. New York State Department of Health AIDS Institute. Ambulatory Care of HIV-Infected Adolescents. 2012. Available at http://hivguidelines.org/wp-content/uploads/2012/11/ambulatory-care-of-hiv-infected-adolescents-11-19-2012.pdf. Accessed January 6, 2016.
15. Nichols SL, Brummel SS, Smith RA, et al. Executive Functioning in Children and Adolescents With Perinatal HIV Infection. *Pediatr Infect Dis J*. Sep 2015;34(9):969-975. Available at http://www.ncbi.nlm.nih.gov/pubmed/26376309.
16. Rogers A (ed). Pharmacokinetics and pharmacodynamics in adolescents. *J Adolesc Health*. 1994;15:605-678.

17. El-Sadar W, Oleske JM, Agins BD, et al. Evaluation and management of early HIV infection. Clinical Practice Guideline No. 7 (AHCPR Publication No. 94-0572). Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services. 1994.

18. Buchacz K, Rogol AD, Lindsey JC, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. *J Acquir Immune Defic Syndr*. 2003;33(1):56-65. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12792356&query_hl=17&itool=pubmed_docsum.

19. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2017. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed January 15, 2016.

20. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Prevalence and interactions of patient-related risks for nonadherence to antiretroviral therapy among perinatally infected youth in the United States. *AIDS Patient Care STDS*. Feb 2010;24(2):97-104. Available at http://www.ncbi.nlm.nih.gov/pubmed/20059354.

21. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. Mar 2009;23(3):185-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/19866536.

22. MacDonell K, Naar-King S, Huszti H, Belzer M. Barriers to medication adherence in behaviorally and perinatally infected youth living with HIV. *AIDS Behav*. Jan 2013;17(1):86-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/23142855.

23. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *J Acquir Immune Defic Syndr*. Oct 1 2011;58(2):193-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/21826014.

24. Lyon ME, Trexler C, Akpan-Townsend C, et al. A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project. *AIDS Patient Care STDS*. Jun 2003;17(6):299-308. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12880493.

25. Belzer ME, Kolmodin MacDonell K, Clark LF, et al. Acceptability and Feasibility of a Cell Phone Support Intervention for Youth Living with HIV with Nonadherence to Antiretroviral Therapy. *AIDS Patient Care STDS*. Jun 2015;29(6):338-345. Available at http://www.ncbi.nlm.nih.gov/pubmed/25928772.

26. Brooks-Gunn J, Graber JA. Puberty as a biological and social event: implications for research on pharmacology. *J Adolesc Health*. Dec 1994;15(8):663-671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7696287.

27. Kyngas H, Hentinen M, Barlow JH. Adolescents' perceptions of physicians, nurses, parents and friends: help or hindrance in compliance with diabetes self-care? *J Adv Nurs*. Apr 1998;27(4):760-769. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9578206.

28. La Greca AM. Peer influences in pediatric chronic illness: an update. *J Pediatr Psychol*. Dec 1992;17(6):775-784. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1484338.

29. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care*. Feb 2001;13(1):27-40. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11177463.

30. Stenzel MS, McKenzie M, Mitty JA, Flanigan TP. Enhancing adherence to HAART: a pilot program of modified directly observed therapy. *AIDS Read*. Jun 2001;11(6):317-319, 324-318. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11449925.

31. Purdy JB, Freeman AF, Martin SC, et al. Virologic response using directly observed therapy in adolescents with HIV: an adherence tool. J Assoc Nurses *AIDS Care*. Mar-Apr 2008;19(2):158-165. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18328966.

32. Garvie PA, Lawford J, Flynn PM, et al. Development of a directly observed therapy adherence intervention for

adolescents with human immunodeficiency virus-1: application of focus group methodology to inform design, feasibility, and acceptability. *J Adolesc Health*. Feb 2009;44(2):124-132. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19167660.

33. Gaur AH, Belzer M, Britto P, et al. Directly observed therapy (DOT) for nonadherent HIV-infected youth: lessons learned, challenges ahead. *AIDS Res Hum Retroviruses*. Sep 2010;26(9):947-953. Available at http://www.ncbi.nlm.nih.gov/pubmed/20707731.
34. Vermund SH, Wilson CM, Rogers AS, Partlow C, Moscicki AB. Sexually transmitted infections among HIV infected and HIV uninfected high-risk youth in the REACH study. Reaching for Excellence in Adolescent Care and Health. *J Adolesc Health*. Sep 2001;29(3 Suppl):49-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/11530303.
35. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. Dec 17 2010;59(RR-12):1-110. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21160459.
36. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*. 2017. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed January 15, 2016.
37. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children*. 2016. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed January 15, 2016.
38. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. 2016. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed January 15, 2016.
39. Valenzuela JM, Buchanan CL, Radcliffe J, et al. Transition to adult services among behaviorally infected adolescents with HIV--a qualitative study. *J Pediatr Psychol*. Mar 2011;36(2):134-140. Available at http://www.ncbi.nlm.nih.gov/pubmed/19542198.
40. Committee On Pediatric A. Transitioning HIV-infected youth into adult health care. *Pediatrics*. Jul 2013;132(1):192-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/23796739.

HIV and People Who Use Illicit Drugs (Last updated March 27, 2012; last reviewed March 27, 2012)

Treatment Challenges in People with HIV Who Use Illicit Drugs

Injection drug use is the second most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate [i.e., poppers]). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among individuals who have HIV infection or who are at risk of HIV infection. The association between club drugs and high-risk sexual behavior in men who have sex with men (MSM) is strongest for methamphetamine and amyl nitrate; this association is less consistent with the other club drugs.[1]

Illicit drug use has been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes.[2] Treatment of HIV disease in people who use illicit drugs can be successful, but this group presents special treatment challenges. These challenges may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment.[3]

Underlying health problems in people who use injection and/or noninjection drugs result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis (TB), skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in people with HIV who use illicit drugs than in people who use illicit drugs and do not have HIV, due in part to respiratory, hepatic, and neurological impairments associated with HIV infection.[4] Success of antiretroviral therapy (ART) in people with HIV who use illicit drugs often depends on clinicians becoming familiar with and managing these comorbid conditions and providing overdose prevention support.

People with HIV who use illicit drugs have less access to HIV care and are less likely to receive ART than other populations.[5-6] Factors associated with low rates of ART use among people who use illicit drugs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and health care providers' lack of expertise in HIV treatment.[5-6] The typically unstable, chaotic life patterns of many people who use illicit drugs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence.[7] The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and people who use illicit drugs.[8-9] The first step in provision of care and treatment for these individuals is to recognize the existence of a substance use problem. It is often obvious that the problem exists, but some patients may hide these problem behaviors from clinicians. Assessment of a patient for a substance use disorder should be part of routine medical history taking and should be done in a professional, straightforward, and nonjudgmental manner.

Treatment Efficacy in Populations of People Who Use Illicit Drugs

Although people who use illicit drugs are underrepresented in HIV therapy clinical trials, available data indicate that efficacy of ART in people who use illicit drugs—when they are not actively using drugs—is similar to that seen in other populations.[10] Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use per se.[11] Providers need to remain attentive to the possible impact of disruptions caused by drug use on the patient both before and while receiving ART. Although many people who use illicit drugs can sufficiently control their drug use for a long enough time to benefit from care, treatment for substance use disorders is often necessary for successful HIV management.

Successful HIV treatment requires close collaboration with treatment programs for substance use disorders and proper support and attention to this population's special multidisciplinary needs. HIV care sites should be accommodating, flexible, and community-based, with experience in managing a wide array of needs for people who use drugs. HIV care sites must also have experience in developing effective strategies to promote medication adherence.[9] These strategies should include, if available, the use of adherence support mechanisms such as modified directly observed therapy (mDOT), which has shown promise among people with HIV who use illicit drugs.[12]

Antiretroviral Agents and Opioid Substitution Therapy

Compared with people receiving ART who do not use illicit drugs, people who use illicit drugs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal (GI), and hematologic disorders are highly prevalent among people who use injection drugs. These comorbid conditions should be considered when selecting antiretroviral (ARV) agents in this population. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended-release naltrexone are commonly used for management of opioid dependence in patients with HIV.

Methadone and Antiretroviral Therapy. Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur.[13] These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. Patients and substance abuse treatment facilities should be informed of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved.

Buprenorphine and Antiretroviral Therapy. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is increasingly used for opioid dependence treatment. Compared with methadone, buprenorphine has a lower risk of respiratory depression and overdose. This allows physicians in primary care to prescribe buprenorphine for the treatment of opioid dependency. The flexibility of the primary care setting can be of significant value to patients with HIV and opioid addiction who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and ARV agents.[13-14] Findings from available studies show that the drug interaction profile of buprenorphine is more favorable than that of methadone.

Naltrexone and Antiretroviral Therapy. A once-monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid

detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[15]

Currently available pharmacokinetic (PK) interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine can be found in Tables 18a-d. Effective communication between HIV care providers and drug treatment programs is essential to prevent additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported.[16]

Summary

It is usually possible over time to support most people with HIV who actively use drugs such that acceptable adherence levels with ARV agents can be achieved.[17-18] Providers must work to combine all available resources to stabilize someone who actively uses drugs in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment and needle and syringe exchange programs, strategies to reduce high-risk sexual behavior, and harm-reduction strategies. A history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to those who do not use drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include need for supportive clinical sites, linkage to substance abuse treatment, and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

References

1. Colfax G, Guzman R. Club drugs and HIV infection: a review. *Clin Infect Dis*. May 15 2006;42(10):1463-1469. Available at https://www.ncbi.nlm.nih.gov/pubmed/16619161.
2. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med*. May 2003;114(7):573-580. Available at https://www.ncbi.nlm.nih.gov/pubmed/12753881.
3. Bruce RD, Altice FL, Gourevitch MN, Friedland GH. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr*. Apr 15 2006;41(5):563-572. Available at https://www.ncbi.nlm.nih.gov/pubmed/16652030.
4. Wang C, Vlahov D, Galai N, et al. The effect of HIV infection on overdose mortality. *AIDS*. Jun 10 2005;19(9):935-942. Available at https://www.ncbi.nlm.nih.gov/pubmed/15905674.
5. Strathdee SA, Palepu A, Cornelisse PG, et al. Barriers to use of free antiretroviral therapy in injection drug users. *JAMA*. Aug 12 1998;280(6):547-549. Available at https://www.ncbi.nlm.nih.gov/pubmed/9707146.
6. Celentano DD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self-reported antiretroviral therapy in injection drug users. *JAMA*. Aug 12 1998;280(6):544-546. Available at https://www.ncbi.nlm.nih.gov/pubmed/9707145.
7. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr*. Sep 01 2001;28(1):47-58. Available at https://www.ncbi.nlm.nih.gov/pubmed/11579277.
8. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *Lancet*. Jul 31 2010;376(9738):367-387. Available at

https://www.ncbi.nlm.nih.gov/pubmed/20650518.

9. Bruce RD, Altice FL, Friedland GH, Volberding P. HIV Disease Among Substance Misusers: Treatment Issues. *Global AIDS/HIV Medicine*. San Diego, CA: Elsevier Ince; 2007:513-526.
10. Morris JD, Golub ET, Mehta SH, Jacobson LP, Gange SJ. Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts. *AIDS Res Ther*. Jun 06 2007;4:12. Available at https://www.ncbi.nlm.nih.gov/pubmed/17553140.
11. Bouhnik AD, Chesney M, Carrieri P, et al. Nonadherence among HIV-infected injecting drug users: the impact of social instability. *J Acquir Immune Defic Syndr*. Dec 15 2002;31 Suppl 3:S149-153. Available at https://www.ncbi.nlm.nih.gov/pubmed/12562040.
12. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis*. Sep 15 2007;45(6):770-778. Available at https://www.ncbi.nlm.nih.gov/pubmed/17712763.
13. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Curr HIV/AIDS Rep*. Aug 2010;7(3):152-160. Available at https://www.ncbi.nlm.nih.gov/pubmed/20532839.
14. Bruce RD, McCance-Katz E, Kharasch ED, Moody DE, Morse GD. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. *Clin Infect Dis*. Dec 15 2006;43 Suppl 4:S216-223. Available at https://www.ncbi.nlm.nih.gov/pubmed/17109308.
15. Food and Drug Administration (FDA). Vivitrol (package insert). 2015.
16. Bruce RD, Altice FL, Friedland GH. Pharmacokinetic drug interactions between drugs of abuse and antiretroviral medications: implications and management for clinical practice. *Expert Rev Clin Pharmacol*. Jan 2008;1(1):115-127. Available at https://www.ncbi.nlm.nih.gov/pubmed/24410515.
17. Hicks PL, Mulvey KP, Chander G, et al. The impact of illicit drug use and substance abuse treatment on adherence to HAART. *AIDS Care*. Oct 2007;19(9):1134-1140. Available at https://www.ncbi.nlm.nih.gov/pubmed/18058397.
18. Cofrancesco J, Jr., Scherzer R, Tien PC, et al. Illicit drug use and HIV treatment outcomes in a US cohort. *AIDS*. Jan 30 2008;22(3):357-365. Available at https://www.ncbi.nlm.nih.gov/pubmed/18195562.

Women with HIV (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all women living with HIV to improve their health and to reduce the risk of HIV transmission to HIV-uninfected sex partners **(AI)**.
- In pregnant women, an additional goal of therapy is to maintain a viral load below the limit of detection throughout pregnancy to reduce the risk of transmission to the fetus and newborn **(AI)**.
- When selecting an antiretroviral (ARV) combination regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and pharmacokinetic (PK) data on use during pregnancy for each agent. The risks and benefits of ARV use during pregnancy should be discussed with all women **(AIII)**.
- For women taking ARV drugs that have significant PK interactions with hormonal contraceptives, an alternative or additional effective contraceptive method to prevent unintended pregnancy is recommended **(AIII)**. Switching to an ARV drug without interactions with hormonal contraceptives may also be considered **(BIII)**.
- Nonpregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (EFV) and receive counseling about the potential risk to the fetus and desirability of avoiding conception while on EFV-based regimens **(AIII)**.
- When designing a regimen for a pregnant woman, clinicians should consult the most current Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines) **(AIII)**.
- Regimens that do not include EFV should be considered in women who are planning to become pregnant or are sexually active and not using effective contraception **(BIII)**.
- Women on a suppressive regimen containing EFV who become pregnant and present to antenatal care during the first trimester can continue EFV throughout pregnancy **(CIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

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 discusses some unique issues to consider and basic principles to follow when caring for women living with HIV, including during pregnancy. Clinicians who care for pregnant women should consult the current Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines) for a more in-depth discussion and guidance on managing these patients.

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown gender differences in virologic responses to antiretroviral therapy (ART).[1-4] However, there are limited data showing that pharmacokinetics (PKs) for some antiretroviral (ARV) drugs may differ between men and women, possibly because of variations between men and women in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.[5-7]

Adverse Effects

Several studies have suggested that gender 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 (NVP) use,[8,9] and are more likely to develop symptomatic lactic acidosis with prolonged use of older nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (ZDV), stavudine (d4T), and didanosine (ddI).[10] These agents are no longer recommended for use in people with HIV in the United States; although ZDV is still administered intravenously (IV) to women during delivery, it is not generally recommended for long-term use.

Some studies have compared women and men in relation to metabolic complications associated with ARV use. Over 96 weeks following initiation of ART, women with HIV are less likely to have decreases in limb fat but more likely to have decreases in bone mineral density (BMD) than men with HIV.[11,12] Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.[13-16] ART 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 containing other NRTIs and raltegravir (RAL).[17-20] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide (TAF; a new oral tenofovir prodrug that induces less bone loss than TDF) may be considered as alternatives to TDF in patients who are at risk of osteopenia or osteoporosis. Recommendations for management of bone disease in people with HIV have been published.[21]

Women with HIV of Childbearing Potential

All women with HIV 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 sex partner(s), and use of effective contraception to prevent unintended pregnancy. Counseling should also include discussion of special considerations pertaining to ARV use when using hormonal contraceptives, when trying to conceive, and during pregnancy (see the Perinatal Guidelines).

Reproductive Options for Serodiscordant Couples

A women who wishes to conceive with a serodiscordant male partner 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 (STIs), ART to maximally suppress and maintain the viral load of the partner with HIV, use of pre-exposure prophylaxis by the uninfected partner,[22-24] male circumcision, and/or self-insemination with the HIV-uninfected partner's sperm during the periovulatory period of the woman with HIV.[25]

Efavirenz (EFV) is teratogenic in nonhuman primates. Nonpregnant women of childbearing potential should have a pregnancy test before starting EFV and be advised of potential EFV-related risks to the fetus and the desirability of avoiding conception while on an EFV-based regimen **(AIII)**. Regimens that do not include EFV should be considered in women who are planning to become pregnant or who are sexually active and not using effective contraception **(BIII)**. The most vulnerable period in fetal organogenesis is early in gestation, usually before pregnancy is recognized. Efavirenz use after the first 8 weeks of pregnancy appears safe.

Hormonal Contraception

Safe and effective reproductive health and family planning services to prevent unintended pregnancies and perinatal transmission of HIV are an essential component of care for women with HIV of childbearing age. These women should receive ongoing counseling on reproductive issues. Regardless of hormonal contraceptive use, women with HIV should be advised to consistently use condoms (male or female) during sex and adhere to an HIV regimen that effectively maintains viral suppression. Both strategies are crucial to prevent transmission of HIV to uninfected partners and to protect against infection with other STIs. The following are some considerations when hormonal contraceptives are used.

Drug-Drug Interactions

PK interactions between ARV drugs and hormonal contraceptives may reduce contraceptive efficacy. However, there are limited clinical data regarding drug interactions between ARVs and hormonal contraceptives and the clinical implications of these interactions are unclear. The magnitudes of changes in drug levels that may reduce contraceptive efficacy or increase adverse effects are unknown.

- **Combined Oral Contraceptives (COCs):** Several PIs, EFV, and elvitegravir/cobicistat (EVG/c)-

based regimens have drug interactions with COCs. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 18a, 18b, and 18d), which potentially decreases contraceptive efficacy or increases estrogen- or progestin-related adverse effects (e.g., thromboembolism). EFV can decrease etonogestrel bioavailability and plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.[26] Several PI/r and EVG/c decrease oral contraceptive estradiol levels.[27-30] Several PK studies have shown that ETR, RPV, and NVP use did not significantly affect estradiol or progestin levels in women with HIV using COCs.[31-33]

- **Injectable Contraceptives:** Small studies of women with HIV receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, lopinavir/ritonavir (LPV/r), NVP, nelfinavir (NFV), or NRTI drugs.[34-37]
- **Contraceptive Implants:** Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported.[38,39] Studies of women with levonorgestrel- and etonogestrel-releasing implants reported that participants receiving EFV-based ART had decreased bioavailability of levonorgestrel and etonogestrel.[40,41] These PK studies did not identify any change in hormone concentrations when the implants were used in women taking NVP[40] or LPV/r.[41] Similarly, two retrospective cohort evaluations conducted in Swaziland and Kenya showed an increased risk of contraceptive failure in women using contraceptive implants and receiving EFV.[42,43]

Concerns about PK interactions between oral or implantable hormonal contraceptives and ARVs should not prevent clinicians from prescribing hormonal contraceptives for women on ART who prefer this contraceptive method. However, an alternative or additional effective contraceptive method is recommended when there are significant drug interactions between hormonal contraceptives and ARVs (see drug interaction Tables 18a, 18b, and 18d and the Perinatal Guidelines).

Risk of HIV Acquisition and Transmission

Studies have produced conflicting data on the association between hormonal contraception and the risk of acquisition of HIV.[44] Most of the retrospective studies were done in the setting where the partners with HIV were not taking ART. A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the partner with HIV was not receiving ART found that women using hormonal contraception (the majority using injectable DMPA) had a two-fold increased risk of acquiring or transmitting HIV. Women with HIV using hormonal contraception had higher genital HIV RNA concentrations than those not using hormonal contraceptives.[45] Oral contraceptive use was not significantly associated with transmission of HIV; however, the number of women using oral contraceptives in this study was insufficient to adequately assess risk. A World Health Organization expert group reviewed all available evidence regarding hormonal contraception and HIV transmission to a partner without HIV and recommended that women living with HIV can continue to use all existing hormonal contraceptive methods without restriction.[46] Further research is needed to definitively determine if hormonal contraceptive use is an independent risk factor for acquisition and transmission of HIV, particularly in the setting of ART. Regardless, the potential association of hormonal contraception use and HIV transmission in the absence of ART underscores the importance of ART-induced viral suppression to reduce transmission risk.

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for women with HIV.[47-49] Although studies have focused primarily on nonhormone-containing IUDs (e.g., copper IUD), several small studies have found that levonorgestrel-releasing IUDs are also safe and not associated with increased genital tract shedding of HIV.[50-52]

Pregnant Women

Clinicians caring for pregnant women with HIV should review the Perinatal Guidelines. The use of combination ARV regimens is recommended for all pregnant women with HIV, regardless of virologic, immunologic, or clinical parameters, for their own health and to prevent transmission of HIV to the fetus

(AI). Pregnant women with HIV should be counseled regarding the known benefits and risks of ARV use during pregnancy to the woman, fetus, and newborn. Women should be counseled and strongly encouraged to receive ART for their own health and that of their infants. Open, nonjudgmental and supportive discussion should be used to encourage women to adhere to care.

Prevention of Perinatal Transmission of HIV

The use of ART and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV.[53-55] The goal of ART is to achieve maximal and sustained viral suppression throughout pregnancy. Long-term follow-up is recommended for all infants born to women who receive ART during pregnancy, regardless of the infant's HIV status (see the Perinatal Guidelines).

ARV Regimen Considerations

Pregnancy should not preclude the use of optimal ARV regimens. As in nonpregnant individuals, genotypic resistance testing is recommended for all pregnant women before ARV initiation **(AIII)** and for pregnant women with detectable HIV RNA while on ART **(AI)**. However, ART initiation should not be delayed in pregnant women pending genotypic resistance testing results. The ARV regimen can be modified, if necessary, once the resistance testing results are available **(BIII)**. Unique considerations that influence recommendations on ARVs to use to treat pregnant women with HIV include the following:

- Physiologic changes associated with pregnancy that potentially result in changes in PKs, which may affect ARV dosing at different stages of pregnancy;
- Potential ARV-associated adverse effects in pregnant women and the potential for adherence to a particular regimen during pregnancy; and
- Potential short- and long-term effects of an ARV on the fetus and newborn, which are unknown for many drugs.

ART is considered the standard of care for pregnant women with HIV, both to treat HIV infection and prevent perinatal transmission of HIV. If a pregnant woman receiving an EFV-based regimen presents to prenatal care during the first trimester with suppressed HIV RNA, EFV can be continued. This is because the risk of fetal neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy. Unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission. Detailed recommendations on ARV choice in pregnancy are discussed in detail in the Perinatal Guidelines.

If maternal HIV RNA is ≥1,000 copies/mL (or unknown) near delivery, IV infusion of ZDV during labor is recommended regardless of the mother's antepartum regimen and resistance profile, and the mode of delivery **(AI)**. Administration of combination ART should continue during labor and before a cesarean delivery (oral medications can be continued with sips of water).

Clinicians who are treating pregnant women with HIV are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (http://www.apregistry.com). The registry collects observational data regarding exposure to Food and Drug Administration (FDA)-approved ARV drugs during pregnancy to assess potential teratogenicity. Analysis of the Antiretroviral Pregnancy Registry data indicates that there is no clear association between first-trimester exposure to any ARV drug and increased risk of birth defects. For more information regarding selection and use of ART during pregnancy, refer to the Perinatal Guidelines.

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for nonpregnant adults and adolescents. Because maternal ART reduces but does not eliminate the risk of

transmission of HIV in breast milk and postnatal transmission can occur despite maternal ART, women should be counseled to avoid breastfeeding.[56] Women with HIV should not premasticate food and feed it to their infants because the practice has been associated with mother-to-child transmission of HIV.[57] ART is currently recommended for all individuals with HIV **(AI)**, therefore maternal ART should be continued after delivery. For more information regarding postpartum management, refer to the Perinatal Guidelines.

Several studies have demonstrated that adherence to ART may decline in the postpartum period.[58-60] Clinicians caring for postpartum women who are receiving ART should address adherence, including an evaluation of specific facilitators and barriers to adherence. Clinicians may recommend an intervention to improve adherence (see Adherence to the Continuum of Care).

References

1. Collazos J, Asensi V, Carton JA. Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART. *AIDS*. Apr 23 2007;21(7):835-843. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17415038.

2. Fardet L, Mary-Krause M, Heard I, Partisani M, Costagliola D. Influence of gender and HIV transmission group on initial highly active antiretroviral therapy prescription and treatment response. *HIV Med*. Nov 2006;7(8):520-529. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17105511.

3. Currier J, Averitt Bridge D, Hagins D, et al. Sex-based outcomes of darunavir-ritonavir therapy: a single-group trial. *Ann Intern Med*. Sep 21 2010;153(6):349-357. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20855799.

4. Rosin C, Elzi L, Thurnheer C, et al. Gender inequalities in the response to combination antiretroviral therapy over time: the Swiss HIV Cohort Study. *HIV Med*. May 2015;16(5):319-325. Available at http://www.ncbi.nlm.nih.gov/pubmed/25329751.

5. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol*. 2004;44:499-523. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14744256.

6. Ofotokun I, Chuck SK, Hitti JE. Antiretroviral pharmacokinetic profile: a review of sex differences. *Gend Med*. Jun 2007;4(2):106-119. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17707845.

7. Venuto CS, Mollan K, Ma Q, et al. Sex differences in atazanavir pharmacokinetics and associations with time to clinical events: AIDS Clinical Trials Group Study A5202. *J Antimicrob Chemother*. Dec 2014;69(12):3300-3310. Available at http://www.ncbi.nlm.nih.gov/pubmed/25159623.

8. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):538-539. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15021321.

9. Wit FW, Kesselring AM, Gras L, et al. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis*. Mar 15 2008;46(6):933-940. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18271750.

10. Lactic Acidosis International Study Group LAISG. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. *AIDS*. Nov 30 2007;21(18):2455-2464. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18025882.

11. McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis*. Jul 15 2011;53(2):185-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/21690627.

12. Galli M, Veglia F, Angarano G, et al. Gender differences in antiretroviral drug-related adipose tissue alterations. Women are at higher risk than men and develop particular lipodystrophy patterns. *J Acquir Immune Defic Syndr*. Sep 1

2003;34(1):58-61. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14501794.

13. Yin M, Dobkin J, Brudney K, et al. Bone mass and mineral metabolism in HIV+ postmenopausal women. *Osteoporos Int*. Nov 2005;16(11):1345-1352. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15754081.

14. Brown TT, Qaqish RB. Response to Berg et al. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. Aug 20 2007;21(13):1830-1831. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17690589.

15. Sharma A, Shi Q, Hoover DR, et al. Increased fracture incidence in middle-aged HIV-infected and HIV-uninfected women: updated results from the Women's Interagency HIV study. *J Acquir Immune Defic Syndr*. Sep 1 2015;70(1):54-61. Available at http://www.ncbi.nlm.nih.gov/pubmed/26322667.

16. Grant PM, Kitch D, McComsey GA, et al. Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. *Clin Infect Dis*. Nov 2013;57(10):1483-1488. Available at http://www.ncbi.nlm.nih.gov/pubmed/23943825.

17. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. Oct 15 2010;51(8):963-972. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20828304.

18. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clin Infect Dis*. Nov 15 2009;49(10):1591-1601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19842973.

19. Duvivier C, Kolta S, Assoumou L, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. *AIDS*. Apr 27 2009;23(7):817-824. Available at http://www.ncbi.nlm.nih.gov/pubmed/19363330.

20. Brown TT, Moser C, Currier JS, et al. Changes in bone mineral density after initiation of antiretroviral treatment with tenofovir disoproxil fumarate/emtricitabine plus atazanavir/ritonavir, darunavir/ritonavir, or raltegravir. *J Infect Dis*. Oct 15 2015;212(8):1241-1249. Available at http://www.ncbi.nlm.nih.gov/pubmed/25948863.

21. Brown TT, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. *Clin Infect Dis*. Apr 15 2015;60(8):1242-1251. Available at http://www.ncbi.nlm.nih.gov/pubmed/25609682.

22. Heffron R, Pintye J, Matthews LT, Weber S, Mugo N. PrEP as peri-conception HIV prevention for women and men. *Curr HIV/AIDS Rep*. Mar 18 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/26993627.

23. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. *AIDS*. Oct 23 2011;25(16):2005-2008. Available at http://www.ncbi.nlm.nih.gov/pubmed/21716070.

24. Whetham J, Taylor S, Charlwood L, et al. Pre-exposure prophylaxis for conception (PrEP-C) as a risk reduction strategy in HIV-positive men and HIV-negative women in the UK. *AIDS Care*. 2014;26(3):332-336. Available at http://www.ncbi.nlm.nih.gov/pubmed/23876052.

25. Lampe MA, Smith DK, Anderson GJ, Edwards AE, Nesheim SR. Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States. *Am J Obstet Gynecol*. Jun 2011;204(6):488 e481-488. Available at http://www.ncbi.nlm.nih.gov/pubmed/21457911.

26. Sevinsky H, Eley T, Persson A, et al. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. *Antivir Ther*. 2011;16(2):149-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/21447863.

27. Vogler MA, Patterson K, Kamemoto L, et al. Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: pharmacokinetic results of ACTG trial A5188. *J Acquir Immune Defic Syndr*. Dec 2010;55(4):473-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/20842042.

28. Zhang J, Chung E, Yones C, et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. *Antivir Ther*. 2011;16(2):157-164. Available at http://

www.ncbi.nlm.nih.gov/pubmed/21447864.

29. Food and Drug Administration. Stribild (package insert). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf. Accessed May 16, 2016. 2016.

30. Food and Drug Administration. Genvoya (package insert). *Gilead*. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207561s000lbl.pdf. Last accessed May 16, 2016.

31. Scholler-Gyure M, Kakuda TN, Woodfall B, et al. Effect of steady-state etravirine on the pharmacokinetics and pharmacodynamics of ethinylestradiol and norethindrone. *Contraception*. Jul 2009;80(1):44-52. Available at http://www.ncbi.nlm.nih.gov/pubmed/19501215.

32. Crauwels HM, van Heeswijk RP, Buelens A, Stevens M, Hoetelmans RM. Lack of an effect of rilpivirine on the pharmacokinetics of ethinylestradiol and norethindrone in healthy volunteers. *Int J Clin Pharmacol Ther*. Feb 2014;52(2):118-128. Available at http://www.ncbi.nlm.nih.gov/pubmed/24161160.

33. Stuart GS, Moses A, Corbett A, et al. Combined oral contraceptives and antiretroviral PK/PD in Malawian women: pharmacokinetics and pharmacodynamics of a combined oral contraceptive and a generic combined formulation antiretroviral in Malawi. *J Acquir Immune Defic Syndr*. Oct 1 2011;58(2):e40-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/21921726.

34. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. Feb 2007;81(2):222-227. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17192768.

35. Nanda K, Amaral E, Hays M, Viscola MA, Mehta N, Bahamondes L. Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy. *Fertil Steril*. Oct 2008;90(4):965-971. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17880953.

36. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception*. Feb 2008;77(2):84-90. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18226670.

37. Luque AE, Cohn SE, Park JG, et al. Depot medroxyprogesterone acetate in combination with a twice-daily lopinavir-ritonavir-based regimen in HIV-infected women showed effective contraception and a lack of clinically significant interactions, with good safety and tolerability: results of the ACTG 5283 study. *Antimicrob Agents Chemother*. Apr 2015;59(4):2094-2101. Available at http://www.ncbi.nlm.nih.gov/pubmed/25624326.

38. Leticee N, Viard JP, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. *Contraception*. Apr 2012;85(4):425-427. Available at http://www.ncbi.nlm.nih.gov/pubmed/22036046.

39. McCarty EJ, Keane H, Quinn K, Quah S. Implanon(R) failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies. *Int J STD AIDS*. Jul 2011;22(7):413-414. Available at http://www.ncbi.nlm.nih.gov/pubmed/21729965.

40. Scarsi KK, Darin KM, Nakalema S, et al. Unintended Pregnancies Observed With Combined Use of the Levonorgestrel Contraceptive Implant and Efavirenz-based Antiretroviral Therapy: A Three-Arm Pharmacokinetic Evaluation Over 48 Weeks. *Clin Infect Dis*. Mar 15 2016;62(6):675-682. Available at http://www.ncbi.nlm.nih.gov/pubmed/26646680.

41. Vieira CS, Bahamondes MV, de Souza RM, et al. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. *J Acquir Immune Defic Syndr*. Aug 1 2014;66(4):378-385. Available at http://www.ncbi.nlm.nih.gov/pubmed/24798768.

42. Patel RC, Onono M, Gandhi M, et al. Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study. *Lancet HIV*. Nov 2015;2(11):e474-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/26520927.

43. Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the Jadelle implant for women living with HIV in a resource-limited setting: concerns for drug interactions leading to unintended pregnancies. *AIDS*. Mar 13 2014;28(5):791-793. Available at http://www.ncbi.nlm.nih.gov/pubmed/24401645.

44. Morrison CS, Nanda K. Hormonal contraception and HIV: an unanswered question. *Lancet Infect Dis*. Jan 2012;12(1):2-3. Available at http://www.ncbi.nlm.nih.gov/pubmed/21975268.

45. Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis*. Jan 2012;12(1):19-26. Available at http://www.ncbi.nlm.nih.gov/pubmed/21975269.

46. World Health Organization. Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statment. Geneva, Switzerland2014. Available at http://apps.who.int/iris/bitstream/10665/128537/1/WHO_RHR_14.24_eng.pdf?ua=1.

47. Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. *Am J Obstet Gynecol*. Aug 2007;197(2):144 e141-148. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17689627.

48. Curtis KM, Nanda K, Kapp N. Safety of hormonal and intrauterine methods of contraception for women with HIV/AIDS: a systematic review. *AIDS*. Nov 2009;23 Suppl 1:S55-67. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20081389.

49. U.S. Medical Eligibility Criteria for Contraceptive Use. Recommendations and Reports June 18, 2010 / 59(RR04);1-6; Prepared by Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion: (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_e). 2010.

50. Heikinheimo O, Lehtovirta P, Aho I, Ristola M, Paavonen J. The levonorgestrel-releasing intrauterine system in human immunodeficiency virus-infected women: a 5-year follow-up study. *Am J Obstet Gynecol*. Feb 2011;204(2):126 e121-124. Available at http://www.ncbi.nlm.nih.gov/pubmed/21035781.

51. Lehtovirta P, Paavonen J, Heikinheimo O. Experience with the levonorgestrel-releasing intrauterine system among HIV-infected women. *Contraception*. Jan 2007;75(1):37-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/17161122.

52. Coleman JS, Mwachari C, Balkus J, et al. Effect of the levonorgestrel intrauterine device on genital HIV-1 RNA shedding among HIV-1-infected women not taking antiretroviral therapy in Nairobi, Kenya. *J Acquir Immune Defic Syndr*. Jun 1 2013;63(2):245-248. Available at http://www.ncbi.nlm.nih.gov/pubmed/23446496.

53. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis*. Feb 15 2001;183(4):539-545. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11170978.

54. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. Aug 5 1999;341(6):385-393. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10432323.

55. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. Aug 5 1999;341(6):394-402. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10432324.

56. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

57. Gaur AH, Freimanis-Hance L, Dominguez K, et al. Knowledge and practice of prechewing/prewarming food by HIV-infected women. *Pediatrics*. May 2011;127(5):e1206-1211. Available at http://www.ncbi.nlm.nih.gov/pubmed/21482608.

58. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr*. Aug 1 2008;48(4):408-417. Available at http://www.ncbi.nlm.nih.gov/pubmed/18614923.

59. Mellins CA, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care*. Sep 2008;20(8):958-968. Available at http://www.ncbi.nlm.nih.gov/pubmed/18608073.

60. Rana AI, Gillani FS, Flanigan TP, Nash BT, Beckwith CG. Follow-up care among HIV-infected pregnant women in Mississippi. *J Womens Health (Larchmt)*. Oct 2010;19(10):1863-1867. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20831428.

HIV-2 Infection (Last updated April 8, 2015; last reviewed April 8, 2015)

Summary of HIV-2 Infection

- Compared to HIV-1 infection, the clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 RNA levels, and lower mortality; however, progression to AIDS does occur.
- There have been no randomized trials addressing the question of when to start antiretroviral therapy (ART) or the choice of initial or second-line therapy for HIV-2 infection; thus, the optimal treatment strategy has not been defined.
- Although the optimal CD4 T lymphocyte (CD4) cell count threshold for initiating ART in HIV-2 infection is unknown, therapy should be started before there is clinical progression.
- HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; thus, these drugs should not be included in an antiretroviral regimen for a patient living with HIV-2 infection.
- Pending more definitive data on outcomes in an ART-naive patient who has HIV-2 mono-infection or HIV-1/HIV-2 dual infection and requires treatment, an initial antiretroviral therapy regimen for these patients should include two nucleoside reverse transcriptase inhibitors plus an HIV-2 active boosted protease inhibitor or integrase strand transfer inhibitors.
- A few laboratories now offer quantitative plasma HIV-2 RNA testing for clinical care (see section text).
- Monitoring of HIV-2 RNA levels, CD4 cell counts, and clinical improvements can be used to assess treatment response, as is recommended for HIV-1 infection.
- Resistance-associated viral mutations to nucleoside reverse transcriptase inhibitors, protease inhibitors, and/or integrase strand transfer inhibitors may develop in patients with HIV-2 while on therapy. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are available for clinical use.
- In the event of virologic, immunologic, or clinical failure, second-line treatment should be instituted in consultation with an expert in HIV-2 management..

HIV-2 infection is endemic in West Africa. Although HIV-2 has had only limited spread outside this area, it should be considered when treating persons of West African origin or in those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high 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).

Clinical Course of HIV-2 Infection

Compared to HIV-1 infection, the clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rate.[1,2] However, HIV-2 infection can also progress to AIDS over time. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from areas with a high prevalence of HIV-2.

Diagnosis of HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot.[3] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable HIV-1 RNA levels or in those with declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on antiretroviral therapy (ART).

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing[4] recommend initial HIV testing using an HIV-1/HIV-2 antigen/antibody combination immunoassay and subsequent testing using an HIV-1/HIV-2 antibody differentiation immunoassay. The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration-approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2.[5,6] Quantitative HIV-2 plasma RNA viral load testing has recently become available for clinical care at the

University of Washington (http://depts.washington.edu/labweb/AboutLM/Contact.htm)[7] and the New York State Department of Health (https://www.wadsworth.org/programs/id/bloodborne-viruses/clinical-testing/hiv-2-nucleic-acid).[8] However, it is important to note that approximately one-quarter to one-third of patients with HIV-2 infection who are not on ART will have HIV-2 RNA levels below the limits of detection; some of these patients will have clinical progression and CD4 cell count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available for clinical use.

Treatment of HIV-2 Infection

To date, no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection have been completed;[9] thus, the optimal treatment strategy has not been defined. Although the optimal CD4 cell count threshold for initiating ART in HIV-2 infection is unknown, therapy should be started before there is clinical progression.

HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTI)[10] and to enfuvirtide (T-20).[11] Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1.[12,13] Darunavir (DRV), lopinavir (LPV), and saquinavir (SQV) are more active against HIV-2 than other approved protease inhibitors (PIs);[14-17] one of these boosted PIs should be used if a PI-based regimen is used. Other PIs should be avoided because of their lack of ARV activity and high failure rates. The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) have potent activity against HIV-2 *in vitro*.[18-21] The CCR5 antagonist maraviroc (MVC) appears active against some HIV-2 isolates;[22] however, no approved assays to determine HIV-2 co-receptor tropism exist and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[23]

Several small studies suggest poor responses in individuals with HIV-2 infection treated with some ARV regimens, including dual-NRTI regimens; regimens containing NNRTI plus two NRTIs; and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine (3TC); and atazanavir (ATV)-based regimens.[9,24-27] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[28,29] In general, HIV-2 active, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses than two or three-NRTI-based regimens.[29-31] However, CD4 cell recovery on therapy is generally poorer than that observed for HIV-1.[31-33] INSTI-based regimens may also have favorable treatment responses.[34,35] A large systematic review of ART for patients with HIV-2 infection (n = 17 studies, 976 patients with HIV-2) was unable to conclude which specific regimens are preferred.[36]

Resistance-associated viral mutations to NRTIs, PIs, and/or INSTIs commonly develop in patients with HIV-2 while on therapy.[24,29,37-41] Currently, HIV-2 transmitted drug resistance appears rare.[41,42] In one small study, DTG was found to have activity as a second-line INSTI in some patients with HIV-2 who had extensive ARV experience and RAL resistance.[43] Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ between the HIV types.[13,29,44]

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection;[45-48] however, currently, there are no controlled trial data to support the effectiveness of the recommended regimens. Pending more definitive data on outcomes in an ART-naive patient who has HIV-2 mono-infection or HIV-1/HIV-2 dual infection and requires treatment, a regimen containing two NRTIs plus an HIV-2 active boosted PI or INSTI should be initiated in individuals with HIV-2 infection.

HIV-2 plasma RNA levels, CD4 cell counts, and clinical improvements can be monitored to assess treatment response, as is recommended for HIV-1. Patients who have HIV-2 RNA levels below the limits of detection before therapy should still have HIV-2 plasma RNA monitoring, in addition to CD4 cell count and clinical monitoring. In the event of virologic, immunologic, or clinical failure, second-line treatment should be

instituted in consultation with an expert in HIV-2 management.

References

1. Matheron S, Pueyo S, Damond F, et al. Factors associated with clinical progression in HIV-2 infected-patients: the French ANRS cohort. *AIDS*. Dec 5 2003;17(18):2593-2601. Available at https://www.ncbi.nlm.nih.gov/pubmed/14685053.
2. Marlink R, Kanki P, Thior I, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science*. Sep 9 1994;265(5178):1587-1590. Available at https://www.ncbi.nlm.nih.gov/pubmed/7915856.
3. O'Brien TR, George JR, Epstein JS, Holmberg SD, Schochetman G. Testing for antibodies to human immunodeficiency virus type 2 in the United States. *MMWR Recomm Rep*. Jul 17 1992;41(RR-12):1-9. Available at https://www.ncbi.nlm.nih.gov/pubmed/1324395.
4. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. 2014. Available at http://stacks.cdc.gov/view/cdc/23447.
5. Chan PA, Wakeman SE, Flanigan T, Cu-Uvin S, Kojic E, Kantor R. HIV-2 diagnosis and quantification in high-risk patients. *AIDS Res Ther*. 2008;5:18. Available at https://www.ncbi.nlm.nih.gov/pubmed/18700986.
6. Damond F, Benard A, Balotta C, et al. An international collaboration to standardize HIV-2 viral load assays: results from the 2009 ACHI(E)V(2E) quality control study. *J Clin Microbiol*. Oct 2011;49(10):3491-3497. Available at http://www.ncbi.nlm.nih.gov/pubmed/21813718.
7. Chang M, Gottlieb GS, Dragavon JA, et al. Validation for clinical use of a novel HIV-2 plasma RNA viral load assay using the Abbott m2000 platform. *J Clin Virol*. Oct 2012;55(2):128-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/22832059.
8. Styer LM, Miller TT, Parker MM. Validation and clinical use of a sensitive HIV-2 viral load assay that uses a whole virus internal control. *J Clin Virol*. Dec 2013;58 Suppl 1:e127-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/24342472.
9. Gottlieb GS, Eholie SP, Nkengasong JN, et al. A call for randomized controlled trials of antiretroviral therapy for HIV-2 infection in West Africa. *AIDS*. Oct 18 2008;22(16):2069-2072; discussion 2073-2064. Available at https://www.ncbi.nlm.nih.gov/pubmed/18832869.
10. Tuaillon E, Gueudin M, Lemee V, et al. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquir Immune Defic Syndr*. Dec 15 2004;37(5):1543-1549. Available at https://www.ncbi.nlm.nih.gov/pubmed/15577405.
11. Poveda E, Rodes B, Toro C, Soriano V. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses*. Mar 2004;20(3):347-348. Available at https://www.ncbi.nlm.nih.gov/pubmed/15117459.
12. Boyer PL, Sarafianos SG, Clark PK, Arnold E, Hughes SH. Why do HIV-1 and HIV-2 use different pathways to develop AZT resistance? *PLoS Pathog*. Feb 2006;2(2):e10. Available at https://www.ncbi.nlm.nih.gov/pubmed/16485036.
13. Smith RA, Anderson DJ, Pyrak CL, Preston BD, Gottlieb GS. Antiretroviral drug resistance in HIV-2: three amino acid changes are sufficient for classwide nucleoside analogue resistance. *J Infect Dis*. May 1 2009;199(9):1323-1326. Available at https://www.ncbi.nlm.nih.gov/pubmed/19358668.
14. Parkin NT, Schapiro JM. Antiretroviral drug resistance in non-subtype B HIV-1, HIV-2 and SIV. *Antivir Ther*. Feb 2004;9(1):3-12. Available at https://www.ncbi.nlm.nih.gov/pubmed/15040531.
15. Desbois D, Roquebert B, Peytavin G, et al. In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother*. Apr 2008;52(4):1545-1548. Available at https://www.ncbi.nlm.nih.gov/pubmed/18227188.
16. Brower ET, Bacha UM, Kawasaki Y, Freire E. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. *Chem Biol Drug Des*. Apr 2008;71(4):298-305. Available at https://www.ncbi.nlm.nih.gov/pubmed/18312292.
17. Rodes B, Sheldon J, Toro C, Jimenez V, Alvarez MA, Soriano V. Susceptibility to protease inhibitors in HIV-2 primary isolates from patients failing antiretroviral therapy. *J Antimicrob Chemother*. Apr 2006;57(4):709-713. Available at

https://www.ncbi.nlm.nih.gov/pubmed/16464891.

18. Roquebert B, Damond F, Collin G, et al. HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir in vitro. *J Antimicrob Chemother*. Nov 2008;62(5):914-920. Available at https://www.ncbi.nlm.nih.gov/pubmed/18718922.

19. Charpentier C, Larrouy L, Collin G, et al. In-vitro phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitor S/GSK1349572. *AIDS*. Nov 13 2010;24(17):2753-2755. Available at http://www.ncbi.nlm.nih.gov/pubmed/20827161.

20. Smith RA, Raugi DN, Pan C, et al. Three main mutational pathways in HIV-2 lead to high-level raltegravir and elvitegravir resistance: implications for emerging HIV-2 treatment regimens. *PLoS One*. 2012;7(9):e45372. Available at http://www.ncbi.nlm.nih.gov/pubmed/23028968.

21. Smith RA, Raugi DN, Pan C, et al. In vitro activity of dolutegravir against wild-type and integrase inhibitor-resistant HIV-2. *Retrovirology*. Feb 05 2015;12:10. Available at http://www.ncbi.nlm.nih.gov/pubmed/25808007.

22. Visseaux B, Charpentier C, Hurtado-Nedelec M, et al. In vitro phenotypic susceptibility of HIV-2 clinical isolates to CCR5 inhibitors. *Antimicrob Agents Chemother*. Jan 2012;56(1):137-139. Available at http://www.ncbi.nlm.nih.gov/pubmed/22064539.

23. Owen SM, Ellenberger D, Rayfield M, et al. Genetically divergent strains of human immunodeficiency virus type 2 use multiple coreceptors for viral entry. *J Virol*. Jul 1998;72(7):5425-5432. Available at https://www.ncbi.nlm.nih.gov/pubmed/9620997.

24. Gottlieb GS, Badiane NM, Hawes SE, et al. Emergence of multiclass drug-resistance in HIV-2 in antiretroviral-treated individuals in Senegal: implications for HIV-2 treatment in resouce-limited West Africa. *Clin Infect Dis*. Feb 15 2009;48(4):476-483. Available at https://www.ncbi.nlm.nih.gov/pubmed/19143530.

25. Jallow S, Kaye S, Alabi A, et al. Virological and immunological response to Combivir and emergence of drug resistance mutations in a cohort of HIV-2 patients in The Gambia. *AIDS*. Jun 26 2006;20(10):1455-1458. Available at https://www.ncbi.nlm.nih.gov/pubmed/16791023.

26. Adje-Toure CA, Cheingsong R, Garcia-Lerma JG, et al. Antiretroviral therapy in HIV-2-infected patients: changes in plasma viral load, CD4+ cell counts, and drug resistance profiles of patients treated in Abidjan, Cote d'Ivoire. *AIDS*. Jul 2003;17 Suppl 3:S49-54. Available at https://www.ncbi.nlm.nih.gov/pubmed/14565609.

27. Cavaco-Silva J, Aleixo MJ, Van Laethem K, et al. Mutations selected in HIV-2-infected patients failing a regimen including atazanavir. *J Antimicrob Chemother*. Jan 2013;68(1):190-192. Available at http://www.ncbi.nlm.nih.gov/pubmed/22977160.

28. Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: results from the French ANRS CO5 HIV-2 cohort. *AIDS*. Feb 14 2006;20(3):459-462. Available at https://www.ncbi.nlm.nih.gov/pubmed/16439883.

29. Ruelle J, Roman F, Vandenbroucke AT, et al. Transmitted drug resistance, selection of resistance mutations and moderate antiretroviral efficacy in HIV-2: analysis of the HIV-2 Belgium and Luxembourg database. *BMC Infect Dis*. 2008;8:21. Available at https://www.ncbi.nlm.nih.gov/pubmed/18304321.

30. Benard A, Damond F, Campa P, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. *AIDS*. Jun 1 2009;23(9):1171-1173. Available at https://www.ncbi.nlm.nih.gov/pubmed/19349850.

31. Ekouevi DK, Balestre E, Coffie PA, et al. Characteristics of HIV-2 and HIV-1/HIV-2 Dually Seropositive Adults in West Africa Presenting for Care and Antiretroviral Therapy: The IeDEA-West Africa HIV-2 Cohort Study. *PLoS One*. 2013;8(6):e66135. Available at http://www.ncbi.nlm.nih.gov/pubmed/23824279.

32. Drylewicz J, Matheron S, Lazaro E, et al. Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France. *AIDS*. Feb 19 2008;22(4):457-468. Available at https://www.ncbi.nlm.nih.gov/pubmed/18301058.

33. Drylewicz J, Eholie S, Maiga M, et al. First-year lymphocyte T CD4+ response to antiretroviral therapy according to the HIV type in the IeDEA West Africa collaboration. *AIDS*. Apr 24 2010;24(7):1043-1050. Available at http://www.ncbi.nlm.

nih.gov/pubmed/20397306.

34. Peterson K, Ruelle J, Vekemans M, Siegal FP, Deayton JR, Colebunders R. The role of raltegravir in the treatment of HIV-2 infections: evidence from a case series. *Antivir Ther*. 2012;17(6):1097-1100. Available at http://www.ncbi.nlm.nih.gov/pubmed/22892365.

35. Zheng Y, Lambert C, Arendt V, Seguin-Devaux C. Virological and immunological outcomes of elvitegravir-based regimen in a treatment-naive HIV-2-infected patient. *AIDS*. Sep 24 2014;28(15):2329-2331. Available at http://www.ncbi.nlm.nih.gov/pubmed/25313590.

36. Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. *BMC Infect Dis*. 2014;14:461. Available at http://www.ncbi.nlm.nih.gov/pubmed/25154616.

37. Damond F, Matheron S, Peytavin G, et al. Selection of K65R mutation in HIV-2-infected patients receiving tenofovir-containing regimen. *Antivir Ther*. Aug 2004;9(4):635-636. Available at https://www.ncbi.nlm.nih.gov/pubmed/15456096.

38. Raugi DN, Smith RA, Ba S, et al. Complex patterns of protease inhibitor resistance among antiretroviral treatment-experienced HIV-2 patients from Senegal: implications for second-line therapy. *Antimicrob Agents Chemother*. Jun 2013;57(6):2751-2760. Available at http://www.ncbi.nlm.nih.gov/pubmed/23571535.

39. Charpentier C, Eholie S, Anglaret X, et al. Genotypic resistance profiles of HIV-2-treated patients in West Africa. *AIDS*. May 15 2014;28(8):1161-1169. Available at http://www.ncbi.nlm.nih.gov/pubmed/24583671.

40. Charpentier C, Roquebert B, Delelis O, et al. Hot spots of integrase genotypic changes leading to HIV-2 resistance to raltegravir. *Antimicrob Agents Chemother*. Mar 2011;55(3):1293-1295. Available at http://www.ncbi.nlm.nih.gov/pubmed/21189351.

41. Charpentier C, Camacho R, Ruelle J, et al. HIV-2EU: supporting standardized HIV-2 drug resistance interpretation in Europe. *Clin Infect Dis*. Jun 2013;56(11):1654-1658. Available at http://www.ncbi.nlm.nih.gov/pubmed/23429380.

42. Charpentier C, Visseaux B, Benard A, et al. Transmitted drug resistance in French HIV-2-infected patients. *AIDS*. Jun 19 2013;27(10):1671-1674. Available at http://www.ncbi.nlm.nih.gov/pubmed/23595155.

43. Descamps D, Peytavin G, Visseaux B, et al. Dolutegravir in HIV-2 infected patients with resistant virus to first-line integrase inhibitors from the French Named Patient Program. *Clin Infect Dis*. Feb 17 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/25690598.

44. Gilleece Y, Chadwick DR, Breuer J, et al. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med*. Nov 2010;11(10):611-619. Available at https://www.ncbi.nlm.nih.gov/pubmed/20961377.

45. New York State Department of Health AIDS Institute. Human Immunodeficiency Virus Type 2 (HIV-2). 2012. Available at http://www.hivguidelines.org/wp-content/uploads/2014/01/human-immunodeficiency-virus-type-2-hiv-2-archived-01-27-2014.pdf.

46. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating And Preventing HIV Infection. 2013. Available at http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf.

47. Expert Group on the Medical Management of HIV Infected Individuals. French HIV-2 Guidelines. Ministry of Health and Sports;2010. Available at http://www.sante.gouv.fr/IMG/pdf/Rapport_2010_sur_la_prise_en_charge_medicale_des_personnes_infectees_par_le_VIH_sous_la_direction_du_Pr-_Patrick_Yeni.pdf.

48. World Health Organization. What ARV regimen to start with in adults adolescents and pregnant women living with HIV-2?. 2013. Available at http://apps.who.int/iris/bitstream/10665/90772/1/WHO_HIV_2013.36_eng.pdf?ua=1.

HIV and the Older Patient (Last updated January 28, 2016; last reviewed January 28, 2016)

Key Considerations When Caring for Older Patients With HIV
• Antiretroviral therapy (ART) is recommended for all patients regardless of CD4 T lymphocyte cell count **(AI)**. ART is especially important for older patients because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART. • Adverse drug events from ART and concomitant drugs may occur more frequently in older patients living with HIV than in younger patients with HIV. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older patients should be monitored closely. • Polypharmacy is common in older patients 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. • HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older patients with HIV with complex comorbidities. • Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older patient with HIV.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
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*

Effective antiretroviral therapy (ART) has increased survival in individuals with HIV, resulting in an increasing number of older individuals living with HIV. In the United States, among persons living with HIV at year-end 2013, 42% were age 50 years or older, 6% were age 65 or older, and trends suggest that these proportions will increase steadily.[1] Care of patients with HIV increasingly will involve adults 60 to 80 years of age, a population for which data from clinical trials or pharmacokinetic (PK) studies are very limited.

There are several distinct areas of concern regarding the association between age and HIV disease.[2] First, older patients with HIV may suffer from aging-related comorbid illnesses that can complicate the management of HIV infection. Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of clinical syndromes generally associated with advanced age. Third, reduced mucosal and immunologic defenses (such as 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 could lead to increased risk of acquisition and transmission of HIV.[3,4] Finally, because older adults are generally perceived to be at low risk of acquiring HIV, screening for this population remains low.

HIV Diagnosis and Prevention in the Older Adult

In older adults, failure to consider a diagnosis of HIV likely contributes to later initiation of ART.[5] The Centers for Disease Control and Prevention (CDC) estimates that in 2013, 37% of adults aged 55 years or older at the time of HIV diagnosis met the case definition for AIDS. The comparable CDC estimates are 18% for adults aged 25 to 34 years and 30% for adults aged 35 to 44 years.[6] In one observational cohort, older patients (defined as those ≥35 years of age) appeared to have lower CD4 T lymphocyte (CD4) cell counts at seroconversion, steeper CD4 count decline over time,[7] and tended to present to care with significantly lower CD4 counts.[8] When individuals >50 years of age present with severe illnesses, 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.[9,10] Despite CDC guidelines recommending HIV testing at least

once in individuals aged 13 to 64, and more frequently for those at risk,[11] HIV testing prevalence remains low (<5%) among adults aged 50 to 64, and decreased with increasing age.[12] Clinicians must be attuned to the possibility of HIV infection in older adults, including those older than 64 years of age and especially in those who may engage in high-risk behaviors. Sexual history taking is therefore an important component of general health care for older adults who do not have HIV, together with risk-reduction counseling, and screening for HIV and sexually transmitted infections (STIs), if indicated.

Impact of Age on HIV Disease Progression

HIV infection presents unique challenges in aging adults and these challenges may be compounded by ART:

- HIV infection itself is thought to induce immune-phenotypic changes akin to accelerated aging,[13] but recent laboratory and clinical data provide a more nuanced view of these changes. Some studies have shown that patients with HIV may exhibit chromosomal and immunologic features similar to those induced by aging.[14,15] However, other studies show the immunologic changes to be distinct from age-related changes.[16] In addition, although data on the increased incidence and prevalence of age-associated comorbidities in patients with HIV are accumulating,[17,18] the age of diagnosis for myocardial infection and non-AIDS cancers in patients who have HIV and those who do not is the same.[18,19]
- Older patients with HIV have a greater incidence of 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,[20] although the phenotype is still incompletely characterized in people with HIV.

Initiating Antiretroviral Therapy in the Older Patient with HIV

ART is recommended for all individuals with HIV (**AI**; see Initiation of Antiretroviral Therapy section). 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. 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 (patients between ages 45 and 65 years).[21] No data support a preference for any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of patient age. The choice of regimen should instead be informed by a comprehensive review of the patient's other medical conditions and medications. The What to Start section (Table 7) of these guidelines provides guidance on selecting an antiretroviral regimen based on an older patient's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older patients with reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix Table 7). In addition, ARV regimen selection may be influenced by potential interaction of antiretroviral medications with drugs used concomitantly to manage comorbidities (see Tables 18a-19b). Adults age >50 years should be monitored for ART effectiveness and safety similarly to other populations with HIV (see Table 3); however, in older patients, special attention should be paid to the greater potential for adverse effects of ART on renal, liver, cardiovascular, metabolic, and bone health (see Table 14).

HIV, Aging, and Antiretroviral Therapy

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 patients. In a recent observational study, a higher rate of viral suppression was seen in patients >55 years old than in younger patients.[22] However, ART-associated CD4 cell recovery in older patients is generally slower and lower in magnitude than in younger patients.[8,23-25] This observation suggests 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.[26] Most clinical trials have included only a small proportion of participants over 50 years of age, and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function. Whether drug accumulation in the older patient may lead to greater incidence and severity of adverse effects than seen in younger patients is unknown.

Patients with HIV and aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management. In addition to taking medications to manage HIV infection and comorbid conditions, many older patients with HIV also are taking medications to relieve discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). They also may self-medicate with over-the-counter medicines or supplements. In older patients who do not have HIV, polypharmacy is a major cause of iatrogenic complications.[27] Some of these complications may be caused by medication errors (by prescribers or patients), medication nonadherence, additive drug toxicities, and drug-drug interactions. Older patients with HIV are probably at an even greater risk of polypharmacy-related adverse consequences than younger or similarly aged patients with HIV. When evaluating any new clinical complaint or laboratory abnormality in patients with HIV, especially in older patients, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.[28] 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 18a-19b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be greater in older patients with HIV than in younger patients with HIV.

Nonadherence is the most common cause of treatment failure. Complex dosing requirements, high pill burden, 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.[32] Although many of these factors associated with nonadherence may be more prevalent in older patients, some studies have shown that older patients with HIV may actually be more adherent to ART than younger patients.[29-31] Clinicians should regularly assess older patients to identify any factors, such as neurocognitive deficits, that may decrease adherence. 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).

Non-AIDS HIV-Related Complications and Other Comorbidities

Among persons treated effectively with ART, as AIDS-related morbidity and mortality have decreased, non-AIDS conditions constitute an increasing proportion of serious illnesses.[33-35] Neurocognitive impairment, already a major health problem in aging adults, may be exacerbated by the effect of HIV infection on the brain.[36] In a prospective observational study, neurocognitive impairment was predictive of lower retention in care among older persons.[37] Neurocognitive impairment probably also affects adherence to therapy. Social isolation and depression are also particularly common among older adults with HIV and, in addition to their direct effects on morbidity and mortality, may contribute to poor medication adherence and retention in care.[38,39] Heart disease and cancer are the leading causes of death in older Americans.[40] Similarly, non-AIDS events such as heart disease, liver disease, and cancer have emerged as major causes of morbidity and mortality in patients with HIV receiving effective ART. The presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection may add to the disease burden of aging adults with HIV.[41-43] HIV-specific primary care guidelines have been updated with recommendations for lipid and

glucose monitoring, evaluation and management of bone health, and management of kidney disease, and are available for clinicians caring for older patients with HIV.[44-48]

Switching, Interrupting, and Discontinuing Antiretroviral Therapy in Older Patients

Given the greater incidence of comorbidities, non-AIDS complications and frailty among older patients 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 women, and suggests switching from tenofovir disoproxil fumarate or boosted protease inhibitors to other ARVs in older patients at high risk for fragility fractures.[45]

Few data exist on the use of ART in severely debilitated patients with chronic, severe, or non-AIDS terminal conditions.[49,50] Withdrawal of ART usually results in rebound viremia and a decline in CD4 cell count. Acute retroviral syndrome after abrupt discontinuation of ART has been reported. In severely debilitated patients, if there are no significant adverse reactions to ART, most clinicians would continue therapy. 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 on the risks and benefits of continuing or withdrawing ART.

Healthcare Utilization, Cost Sharing, and End-of-Life Issues

Important issues to discuss with aging patients with HIV are living wills, advance directives, and long-term care planning, including related financial concerns. 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 the higher prevalence of chronic complications in aging populations with HIV can place greater demands upon HIV services.[51] Facilitating a patient's continued access to insurance can minimize treatment interruptions and reduce the need for other services to manage concomitant chronic disorders.

Conclusion

HIV disease 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 patients with HIV, increasing the number of patients >50 years of age living with HIV. However, unique challenges in this population include greater incidence of complications and comorbidities, and some of these complications 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 patients with HIV is warranted.

References

1. Centers for Disease Control and Prevention. HIV Surveillance Report, 2014; vol. 26. 2015. Available at http://www.cdc.gov/hiv/library/reports/surveillance/. Accessed December 10, 2015.
2. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. 2009;338:a3172. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19171560.
3. Levy JA, Ory MG, Crystal S. HIV/AIDS interventions for midlife and older adults: current status and challenges. *J Acquir Immune Defic Syndr*. Jun 1 2003;33 Suppl 2:S59-67. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12853854.
4. Levy BR, Ding L, Lakra D, Kosteas J, Niccolai L. Older persons' exclusion from sexually transmitted disease risk-reduction clinical trials. *Sex Transm Dis*. Aug 2007;34(8):541-544. Available at http://www.ncbi.nlm.nih.gov/entrez/

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17297381.

5. Althoff KN, Gebo KA, Gange SJ, et al. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? *AIDS Res Ther*. 2010;7:45. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21159161.

6. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2013. HIV Surveillance Supplemental Report 2015;20 (No. 2). 2015. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/. Accessed August 21, 2015.

7. Lodi S, Phillips A, Touloumi G, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm^3: assessment of need following changes in treatment guidelines. *Clin Infect Dis*. Oct 2011;53(8):817-825. Available at http://www.ncbi.nlm.nih.gov/pubmed/21921225.

8. Sabin CA, Smith CJ, d'Arminio Monforte A, et al. Response to combination antiretroviral therapy: variation by age. *AIDS*. Jul 31 2008;22(12):1463-1473. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18614870.

9. Stone VE, Bounds BC, Muse VV, Ferry JA. Case records of the Massachusetts General Hospital. Case 29-2009. An 81-year-old man with weight loss, odynophagia, and failure to thrive. *N Engl J Med*. Sep 17 2009;361(12):1189-1198. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19759382.

10. Ward EG, Disch WB, Schensul JJ, Levy JA. Understanding low-income, minority older adult self-perceptions of HIV risk. *J Assoc Nurses AIDS Care*. Jan-Feb 2011;22(1):26-37. Available at http://www.ncbi.nlm.nih.gov/pubmed/20580270.

11. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. Sep 22 2006;55(RR-14):1-17. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16988643.

12. Ford CL, Godette DC, Mulatu MS, Gaines TL. Recent HIV testing prevalence, determinants, and disparities among U.S. older adult respondents to the behavioral risk factor surveillance system. *Sex Transm Dis*. Aug 2015;42(8):405-410. Available at http://www.ncbi.nlm.nih.gov/pubmed/26165428.

13. Martin J, Volberding P. HIV and premature aging: A field still in its infancy. *Ann Intern Med*. Oct 5 2010;153(7):477-479. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20921548.

14. Liu JC, Leung JM, Ngan DA, et al. Absolute leukocyte telomere length in HIV-infected and uninfected individuals: evidence of accelerated cell senescence in HIV-associated chronic obstructive pulmonary disease. *PLoS One*. 2015;10(4):e0124426. Available at http://www.ncbi.nlm.nih.gov/pubmed/25885433.

15. Zanet DL, Thorne A, Singer J, et al. Association between short leukocyte telomere length and HIV infection in a cohort study: No evidence of a relationship with antiretroviral therapy. *Clin Infect Dis*. May 2014;58(9):1322-1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/24457340.

16. Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PLoS One*. 2014;9(5):e97482. Available at http://www.ncbi.nlm.nih.gov/pubmed/24830290.

17. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis*. Dec 15 2014;59(12):1787-1797. Available at http://www.ncbi.nlm.nih.gov/pubmed/25182245.

18. Althoff KN, McGinnis KA, Wyatt CM, et al. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clin Infect Dis*. Feb 15 2015;60(4):627-638. Available at http://www.ncbi.nlm.nih.gov/pubmed/25362204.

19. Rasmussen LD, May MT, Kronborg G, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. *Lancet HIV*. Jul 2015;2(7):e288-298. Available at http://www.ncbi.nlm.nih.gov/pubmed/26423253.

20. Althoff KN, Jacobson LP, Cranston RD, et al. Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. *J Gerontol A Biol Sci Med Sci*. Feb 2014;69(2):189-198. Available at http://www.ncbi.nlm.nih.gov/pubmed/24127428.

21. Edwards JK, Cole SR, Westreich D, et al. Age at Entry Into Care, Timing of Antiretroviral Therapy Initiation, and 10-Year Mortality Among HIV-Seropositive Adults in the United States. *Clin Infect Dis*. Oct 1 2015;61(7):1189-1195. Available at http://www.ncbi.nlm.nih.gov/pubmed/26082505.

22. Horberg MA, Hurley LB, Klein DB, et al. The HIV Care Cascade Measured Over Time and by Age, Sex, and Race in a Large National Integrated Care System. *AIDS Patient Care STDS*. Nov 2015;29(11):582-590. Available at http://www.ncbi.nlm.nih.gov/pubmed/26505968.

23. Althoff KN, Justice AC, Gange SJ, et al. Virologic and immunologic response to HAART, by age and regimen class. *AIDS*. Oct 23 2010;24(16):2469-2479. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20829678.

24. Bosch RJ, Bennett K, Collier AC, Zackin R, Benson CA. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):268-277. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17146370.

25. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis*. 2006;6:159. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17087819.

26. Sitar DS. Aging issues in drug disposition and efficacy. *Proc West Pharmacol Soc*. 2007;50:16-20. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18605223.

27. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium." *JAMA*. Oct 13 2010;304(14):1592-1601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20940385.

28. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother*. Sep 2011;66(9):2107-2111. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21680580.

29. Wellons MF, Sanders L, Edwards LJ, Bartlett JA, Heald AE, Schmader KE. HIV infection: treatment outcomes in older and younger adults. *J Am Geriatr Soc*. Apr 2002;50(4):603-607. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11982658.

30. Wutoh AK, Elekwachi O, Clarke-Tasker V, Daftary M, Powell NJ, Campusano G. Assessment and predictors of antiretroviral adherence in older HIV-infected patients. *J Acquir Immune Defic Syndr*. Jun 1 2003;33 Suppl 2:S106-114. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12853859.

31. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry CP, Jr. Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med*. Apr 9 2007;167(7):684-691. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17420427.

32. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother*. Feb 2011;9(1):11-23. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21459305.

33. Justice AC. HIV and aging: time for a new paradigm. *Curr HIV/AIDS Rep*. May 2010;7(2):69-76. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20425560.

34. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. Sep 2006;43(1):27-34. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16878047.

35. Smit C, Geskus R, Walker S, et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. *AIDS*. Mar 21 2006;20(5):741-749. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16514305.

36. Vance DE, Wadley VG, Crowe MG, Raper JL, Ball KK. Cognitive and everyday functioning in older and younger adults with and without HIV. *Clinical Gerontologists*. 2011;34(5):413-426.

37. Jacks A, Wainwright DA, Salazar L, et al. Neurocognitive deficits increase risk of poor retention in care among older adults with newly diagnosed HIV infection. *AIDS*. Aug 24 2015;29(13):1711-1714. Available at http://www.ncbi.nlm.nih.gov/pubmed/26372282.

38. Grov C, Golub SA, Parsons JT, Brennan M, Karpiak SE. Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care*. May 2010;22(5):630-639. Available at http://www.ncbi.nlm.nih.gov/pubmed/20401765.

39. Kalichman SC, Heckman T, Kochman A, Sikkema K, Bergholte J. Depression and thoughts of suicide among middle-aged and older persons living with HIV-AIDS. *Psychiatr Serv*. Jul 2000;51(7):903-907. Available at http://www.ncbi.nlm.nih.gov/pubmed/10875956.

40. Kochanek KD, Xu J, Murphy SL, Minino AM, King HC. Deaths: Preliminary data for 2009. *National Vital Statistics Reports*. 2011;59(4):1-54.

41. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. Dec 2011;53(11):1120-1126. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21998278.

42. Capeau J. Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. *Clin Infect Dis*. Dec 2011;53(11):1127-1129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21998279.

43. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis*. Dec 2011;53(11):1130-1139. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21998280.

44. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the *HIV Med*icine association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):e1-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/24235263.

45. Brown TT, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. *Clin Infect Dis*. Apr 15 2015;60(8):1242-1251. Available at http://www.ncbi.nlm.nih.gov/pubmed/25609682.

46. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the *HIV Med*icine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Nov 1 2014;59(9):e96-138. Available at http://www.ncbi.nlm.nih.gov/pubmed/25234519.

47. American Academy of *HIV Med*icine. The HIV and Aging Consensus Project: Recommended treatment strategies for clinicians managing older patients with HIV. 2011. Available at http://www.aahivm.org/Upload_Module/upload/HIV%20and%20Aging/Aging%20report%20working%20document%20FINAL.pdf. Accessed January 13, 2016.

48. Jacobson TA, Maki KC, Orringer CE, al. e. National lipid association recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipidol*. 2015.

49. Selwyn PA. Chapter 75. In: Berger AM S, JL, Von Roenn JH, ed. Palliative care in HIV/AIDS. In Principles and Practice of Palliative Care and Supportive Oncology 3rd Edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2007:833-848.

50. Harding R, Simms V, Krakauer E, et al. Quality HIV Care to the End of life. *Clin Infect Dis*. Feb 15 2011;52(4):553-554; author reply 554. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21258107.

51. Brennan A, Morley D, O'Leary AC, Bergin CJ, Horgan M. Determinants of HIV outpatient service utilization: a systematic review. *AIDS Behav*. Jan 2015;19(1):104-119. Available at http://www.ncbi.nlm.nih.gov/pubmed/24907780.

Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis B/HIV Virus Coinfection (Last updated October 17, 2017; last reviewed October 17, 2017)

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 ART regimen for patients with both HIV and HBV should be include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen **(AI)**.
• If TDF or TAF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen **(BI)**. Entecavir has 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 may also 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 be carefully monitored during interruptions in HBV treatment **(AII)**.
• If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.
• HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment. For that reason, all patients initiating HCV therapy should be tested for HBV. Persons 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 = Optional*
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 persons with HBV/HIV coinfection than in persons 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 (CD4) 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, 3TC or 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, HBV, or both 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 transaminase levels. The rate 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 liver function tests 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. However, increased transaminase levels in persons 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.

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 Infection in the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents). Patients with chronic HBV should also 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 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.
- Since HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment,[16,17] persons 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 persons 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 which also has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicities than TDF.

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; $P = .47$).[18] TAF was also 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; $P = .25$).[19] 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.[18,19]

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 persons 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)**.[20-22] 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. In a switch study in patients with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ART 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.[23] TAF/FTC-containing regimens currently approved for the treatment of HIV infection are not recommended for use in patients with creatinine clearance (CrCl) <30 mL/min. While data on switching from a TDF-based to a TAF-based ART 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 safely be 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).[24] 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 persons 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 may also be considered in some patients with HBV/HIV coinfection. However, data on the use of this therapy in persons with HBV/HIV coinfection are limited and, given safety concerns, peginterferon alfa should not be used in persons 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.[20,25,26] However, data on these regimens in persons 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 HIV-Infected Adults and Adolescents **does not currently recommend** adefovir or telbivudine for patients with HBV/HIV coinfection.

Changing Antiretroviral Therapy

- **Need to discontinue ARV medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. 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] These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.
- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other ARV agents that effectively suppress HIV **(AIII)**.

References

1. Spradling PR, Richardson JT, Buchacz K, Moorman AC, Brooks JT. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. *J Viral Hepat*. Feb 11 2010. Available at https://www.ncbi.nlm.nih.gov/pubmed/20158604.
2. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. Dec 14 2002;360(9349):1921-1926. Available at https://www.ncbi.nlm.nih.gov/pubmed/12493258.
3. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. Mar 24 2005;19(6):593-601. Available at https://www.ncbi.nlm.nih.gov/pubmed/15802978.
4. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. *AIDS*. Sep 10 2009;23(14):1881-1889. Available at https://www.ncbi.nlm.nih.gov/pubmed/19550291.
5. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med*. Jan 2009;10(1):12-18. Available at https://www.ncbi.nlm.nih.gov/pubmed/18795964.
6. Law WP, Dore GJ, Duncombe CJ, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. *AIDS*. Oct 17 2003;17(15):2191-2199. Available at https://www.ncbi.nlm.nih.gov/pubmed/14523276.
7. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. Jul 1 2002;186(1):23-31. Available at https://www.ncbi.nlm.nih.gov/pubmed/12089658.
8. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. *AIDS*. Mar 27 2010;24(6):857-865. Available at https://www.ncbi.nlm.nih.gov/pubmed/20216301.
9. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med*. Jun 21 2007;356(25):2614-2621. Available at https://www.ncbi.nlm.nih.gov/pubmed/17582071.
10. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology*. Nov 1999;30(5):1302-1306. Available at https://www.ncbi.nlm.nih.gov/pubmed/10534354.
11. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis*. Jan 2001;32(1):144-148. Available at https://www.ncbi.nlm.nih.gov/pubmed/11118394.
12. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. Jan 5 2000;283(1):74-80. Available at https://www.ncbi.nlm.nih.gov/pubmed/10632283.
13. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for

hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. Dec 22 2000;14(18):2895-2902. Available at https://www.ncbi.nlm.nih.gov/pubmed/11153671.

14. Neukam K, Mira JA, Collado A, et al. Liver toxicity of current antiretroviral regimens in HIV-infected patients with chronic viral hepatitis in a real-life setting: The HEPAVIR SEG-HEP Cohort. *PLoS One*. 2016;11(2):e0148104. Available at http://www.ncbi.nlm.nih.gov/pubmed/26848975.

15. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the *HIV Medi*cine Association of the Infectious Diseases Society of America. 2016. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

16. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Ann Intern Med*. Jun 06 2017;166(11):792-798. Available at https://www.ncbi.nlm.nih.gov/pubmed/28437794.

17. Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. Jan 2017;15(1):132-136. Available at https://www.ncbi.nlm.nih.gov/pubmed/27392759.

18. Buti M, Gane E, Seto WK, et al. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-negative, chronic hepatitis B: Week 48 efficacy and safety results. Presented at: EASL International Liver Conference. 2016. Barcelona, Spain.

19. Chan HLY, Fung S, Seto WK. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-positive, chronic hepatitis B: Week 48 efficacy and safety results. Presented at: EASL International Liver Conference. 2016. Barcelona, Spain.

20. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. Nov 2006;44(5):1110-1116. Available at https://www.ncbi.nlm.nih.gov/pubmed/17058225.

21. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS*. Aug 24 2009;23(13):1707-1715. Available at https://www.ncbi.nlm.nih.gov/pubmed/19584701.

22. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-term therapy with tenofovir is effective for patients co-infected with HIV and HBV. *Gastroenterology*. Aug 26 2010. Available at https://www.ncbi.nlm.nih.gov/pubmed/20801123.

23. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B coinfected adults. *J Acquir Immune Defic Syndr*. May 11 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/27171740.

24. Pessoa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfected patients receiving lamivudine as part of antiretroviral therapy. *AIDS*. Sep 12 2008;22(14):1779-1787. Available at https://www.ncbi.nlm.nih.gov/pubmed/18753861.

25. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet*. Sep 1 2001;358(9283):718-723. Available at https://www.ncbi.nlm.nih.gov/pubmed/11551579.

26. Ingiliz P, Valantin MA, Thibault V, et al. Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther*. 2008;13(7):895-900. Available at https://www.ncbi.nlm.nih.gov/pubmed/19043923.

Hepatitis C Virus/HIV Coinfection (Last updated October 17, 2017; last reviewed October 17, 2017)

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 persons 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 (CD4) cell count **(AI)**.
- Initial ART regimens recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimen should be selected with special consideration for potential drug-drug interactions and overlapping toxicities (see discussion in the text below and in Table 12).
- In patients with lower CD4 counts (e.g., <200 cells/mm^3), ART should be initiated promptly **(AI)** and HCV therapy may be delayed until the patient is stable on HIV treatment **(CIII)**.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy and have their liver fibrosis stage assessed to inform the length of their therapy, ribavirin need (a concern with some regimens), and subsequent risk of hepatocellular carcinoma and liver disease complications.
- Persons 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 core (HBcAb total or IgG). Persons who are not immune to HBV infection (HBsAb-negative) should receive anti-HBV vaccination **(AIII)**.
- HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment. Accordingly, persons with HCV/HIV coinfection and active HBV infection (HBsAg-positive) 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 = Optional*

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) rates comparable to those of patients with HCV monoinfection.[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 http://www.hcvguidelines.org/.

Among patients with chronic HCV infection, approximately one-third progress to cirrhosis, at a median time of less than 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 three-fold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV monoinfection.[8] The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte (CD4) 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 continues to exceed that observed in patients without HIV infection.[10,11] Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death,[12] is unclear. Although some older ARV drugs were associated with higher rates of hepatotoxicity in patients with chronic HCV infection,[13,14] the newer ARV agents that are currently in use are less hepatotoxic.

Assessment of HCV/HIV Coinfection

- All patients with HIV should be screened for HCV infection using sensitive immunoassays licensed for the detection of antibodies to HCV in blood.[15] At-risk HCV-seronegative patients should undergo repeat

testing annually. HCV-seropositive patients 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 guidelines (see http://www.hcvguidelines.org/).

- Patients with HCV/HIV coinfection should be counseled to avoid consuming alcohol and to use appropriate precautions to prevent transmission of HIV and/or HCV to others.
- People 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 core (HBcAb total or IgG).
  - Persons with evidence of active HBV infection (HBsAg) should be further evaluated and treated with ART that includes agents with anti-HIV and 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.
- 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 persons with HCV/HIV coinfection should follow the recommendations for all persons with HIV infection, taking into account the needs for concurrent HCV treatment with oral DAA regimens and the individual's HBV status.

Antiretroviral Drugs to Start and Avoid

Initial ARV combination regimens recommended for most HIV treatment-naive patients with HCV are the same as those recommended for patients without HCV infection. 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 12).
- HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment.[16,17] Therefore, persons 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 [TAF] plus emtricitabine or lamivudine) prior to initiating HCV therapy **(AIII)**.
- Cirrhotic patients 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 for consideration of 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 7).

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 monoinfection. 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 if clinically indicated. Mild to moderate fluctuations in ALT and/or AST are typical in individuals with chronic HCV infection. In the absence of signs and/or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART. Patients with significant ALT and/or AST elevation should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute hepatitis A virus [HAV] or HBV infection, hepatobiliary disease, or alcoholic hepatitis).

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found at http://www.hcvguidelines.org/. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug-drug interactions when used in combination. Prior to starting HCV therapy, the ART regimen may need to be modified to reduce the drug-drug interaction potential. Table 12 below provides recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection. In patients on modified ART who have suppressed plasma HIV RNA, HIV RNA should be measured within 4 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After HCV treatment is completed, the modified ART regimen should be continued for at least 2 weeks before reinitiating the original regimen. Continued use of the modified regimen is necessary because of the prolonged half-life of some HCV drugs and the potential risk of drug-drug interactions if a prior HIV regimen is resumed soon after HCV treatment is completed.

Table 12. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 1 of 4)

The recommendations in this table for concomitant use of selected HIV drugs with Food and Drug Administration (FDA)-approved hepatitis C virus (HCV) direct-acting antiviral (DAA) drugs are based on available pharmacokinetic interaction data or predictions based on the known metabolic pathway of the agents. In some cases, there are not enough data to make any recommendations, and these instances are indicated in the table. In all cases where HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. As the field of HCV therapy is rapidly evolving, readers should also refer to the latest drug product labels and HCV guidelines (www.hcvguidelines.org/) for updated information.

Note: Interactions with fosamprenavir, indinavir, nelfinavir, and saquinavir are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV protease inhibitors (PIs). Because the HCV PIs boceprevir and telaprevir are no longer recommended for HCV treatment, these products have been removed from this table.

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
				SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Turcotte Pugh class B or C)					
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
NRTIs									
3TC	✔	✔	✔	✔	✔	✔	✔	✔	✔
ABC	✔	✔	✔	✔	✔	✔	✔	✔	✔
FTC	✔	✔	✔	✔	✔	✔	✔	✔	✔
TDF	✔	✔	✔ Monitor for TDF toxicity.	✔ Monitor for TDF toxicity.	✔ Monitor for TDF toxicity.	✔	✔	✔	✔
TAF	✔	✔	✔	✔	✔	✔	✔	✔	✔
PIs									
Unboosted ATV	✔	✔	✔	✔	✘	✘	✘	✔[b]	✘

Table 12. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 2 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
				SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Turcotte Pugh class B or C)					
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
PIs, continued									
ATV/r or ATV/c	✔ ↓ DCV dose to 90 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 toxicities.[d]	✔ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated toxicities.[d]	✘	✘	✘	✔[c]	✘
DRV/r or DRV/c	✔	✔			✔ If a PI/r is used with TDF, ↑TDF concentrations. Monitor for TDF-associated toxicities.[d] Consider monitoring for hepatotoxicity.[e]	✘	✘	✘	✘
LPV/r	✔	✔			✘	✘	✘	✘	✘
TPV/r	?	✘	✘	✘	✘	✘	✘	✘	✘
NNRTIs									
EFV	✔ ↑ DCV dose to 90 mg/day	✔	✔ If used with TDF, monitor for TDF toxicity.	✘	✘	✘	✘	✘	✘
ETR	✔ ↑ DCV dose to 90 mg/day	✔		✘	✘	✘	✘	✘	✘
NVP	✔ ↑ DCV dose to 90 mg/day	✔		✘	✘	?	✘	✘	✘
RPV	✔	✔		✔	✔	✔	✔	✘	✔

Table 12. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 3 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
				SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Turcotte Pugh class B or C)					
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
INSTIs									
DTG	✔	✔	✔ If used with TDF, monitor for TDF toxicity.	✔	✔	✔	✔	✔	✔
EVG/c/TDF/ FTC	✔ ↓ DCV dose to 30 mg/day	✔	✘	✔ If used with TDF, monitor for TDF toxicity.	✔ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[e]	✔ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[f]	✘	✘	✘
EVG/c/TAF/ FTC	✔ ↓ DCV dose to 30 mg/day	✔	✔	✔	✔ Consider monitoring for hepatotoxicity.[e]	✔ Consider monitoring for hepatotoxicity.[f]	✘	✘	✘
RAL	✔	✔	✔	✔	✔	✔	✔	✔	✔
CCR5 Antagonist									
MVC	✔	✔	✔	✔	✔	✔	?	✘	✔

[a] Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir

[b] Reduce ATV dose to 300 mg and take in the morning at same time as ombitasvir/paritaprevir/ritonavir plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.

[c] Take ATV 300 mg in the morning at same time as ombitasvir/paritaprevir/ritonavir plus dasabuvir. If taking RTV or COBI, discontinue RTV or COBI in HIV regimen until HCV therapy is completed.

Table 12. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 4 of 4)

[d] Consider alternative HCV or ART to avoid increases in TDF exposure. If co-administration is necessary, monitor patient for TDF-associated adverse reactions.

[e] Due to increased voxilaprevir exposures when given with pharmacologically boosted DRV or EVG, monitoring patients for hepatotoxicity is recommended until more safety data in clinical settings becomes available.

[f] Due to increased glecaprevir exposures when given with EVG/c, monitoring patients for hepatotoxicity is recommended until more safety data in clinical settings becomes available.

Key to Symbols:

✔ = ARV agents that can be used concomitantly

✘ = ARV agents not recommended

? = data limited or not available on pharmacokinetic interactions with ARV drug

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DAA = direct-acting antiviral agents; DRV = darunavir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; DSV = dasabuvir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HCV = hepatitis C virus; 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 = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

References

1. Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med*. 2015;373(8):705-713. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26196665.
2. Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet* HIV. 2015;2(8):e319-327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26423374.
3. Sogni P, Gilbert C, Lacombe K, et al. All-oral direct-acting antiviral regimens in HIV/hepatitis C virus-coinfected patients with cirrhosis are efficient and safe: real-life results from the prospective ANRS CO13-HEPAVIH cohort. *Clin Infect Dis*. 2016;63(6):763-770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27317796.
4. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. *N Engl J Med*. 1992;327(27):1899-1905. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1280771.
5. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284(4):450-456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10904508.
6. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9121257.
7. Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28(3):805-809. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9731576.
8. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4):562-569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11462196.
9. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS*. 2008;22(15):1979-1991. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18784461.
10. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16908797.
11. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19339714.
12. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet*. 2000;356(9244):1800-1805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11117912.
13. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283(1):74-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10632283.
14. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. 2002;35(1):182-189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11786975.
15. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2017. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0.
16. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration adverse event reporting system. *Ann Intern Med*. 2017;166(11):792-798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28437794.
17. Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. 2017;15(1):132-136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27392759.
18. Aranzabal L, Casado JL, Moya J, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis*. 2005;40(4):588-593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15712082.
19. Labarga P, Soriano V, Vispo ME, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis*. 2007;196(5):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17674307.

Tuberculosis/HIV Coinfection (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations

- Selection of a tuberculosis (TB)-preventive treatment for individuals living with HIV and coinfected with latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral therapy (ART) regimen as noted below:
  - Any ART regimen can be used when isoniazid alone is used for LTBI treatment **(AII)**.
  - Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine **(AIII)**.
  - If rifampin or rifabutin is used to treat LTBI, clinicians should review Tables 18a through 18e to assess the potential for interactions among different antiretroviral (ARV) drugs and the rifamycins **(BIII)**.
- All patients with both HIV and active TB who are not on ART should be started on ART as described below:
  - **In patients with CD4 counts <50 cells/mm^3:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI)**.
  - **In patients with CD4 counts ≥50 cells/mm^3:** Initiate ART within 8 weeks of starting TB treatment **(AIII)**.
  - **In all pregnant women with HIV:** Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV **(AIII)**.
  - **In patients with tuberculous meningitis:** Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial **(AI)**.
- Rifamycins are critical components of TB treatment regimens and should be included for patients with both HIV and active TB, unless precluded because of TB resistance or toxicity. However, rifamycins have a considerable potential for drug-drug interactions. Clinicians should review Tables 18a through 18e to assess the potential for interactions among different ARV drugs and the rifamycins **(BIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

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*

Management of Latent Tuberculosis Infection in HIV-Infected Patients

According to the World Health Organization (WHO), approximately one-third of the world's population is infected with tuberculosis (TB), with a 5% to 10% lifetime risk of progressing to active disease.[1] People with HIV who are coinfected with TB have a much higher risk of developing active TB than individuals who do not have HIV, and this risk increases as immune deficiency worsens.[2]

Anti-Tuberculosis Therapy as Preventive Tuberculosis Treatment

Many clinical trials have demonstrated that treatment for latent tuberculosis infection (LTBI) reduces risk of active TB in people with HIV, especially those with a positive tuberculin skin test.[3] After active TB disease has been excluded, the Centers for Disease Control and Prevention (CDC) recommends one of the following regimens for LTBI treatment (http://www.cdc.gov/tb/topic/treatment/ltbi.htm):

- Isoniazid (INH) daily or twice weekly for 9 months
- INH plus rifapentine once weekly for 12 weeks
- Rifampin (or rifabutin) daily for 4 months

For more than 30 years, INH has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadminstered with any antiretroviral (ARV) regimen and is safe to use in pregnant women. The combination of INH and rifapentine administered weekly for 12 weeks as directly observed therapy (DOT) is another treatment option for LTBI. In the PREVENT TB study, rifapentine plus INH for 12 weeks was as safe and effective as 9 months of INH alone in preventing TB in patients with HIV who were not on ART.[4] There was no difference in TB incidence in 1,148 South African adults with HIV who were randomized to receive rifapentine plus INH weekly for 12 weeks, rifampin plus INH twice weekly for 12 weeks, INH daily for 6 months, or continuous INH therapy.[5] Although rifapentine induces cytochrome P (CYP) 450 isoenzymes and

can potentially cause significant drug-drug interactions, there are now pharmacokinetic (PK) data supporting its use with efavirenz (EFV)[6] and raltegravir (RAL)[7] **(AIII)**. Rifampin or rifabutin for 4 months may also be considered for LTBI treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 18a through 18e).

If a patient with HIV is a contact of an individual with drug-resistant TB, the options for LTBI treatment should be modified. In this setting, consultation with a TB expert is advised.

Antiretroviral Therapy's Effect in Preventing Active Tuberculosis

Accumulating evidence also suggests that ART can prevent active TB. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV who did not meet WHO criteria for ART initiation to one of four study arms: deferred ART (until WHO criteria were met); deferred ART plus INH preventive therapy (IPT); early ART; or early ART plus IPT.[8] Among participants with CD4 T lymphocyte (CD4) counts >500 cells/mm^3, starting ART immediately reduced the risk of death and serious HIV-related illness, including TB, by 44% (2.8 vs. 4.9 severe events per 100 person-years with immediate and deferred ART, respectively; $P = .0002$). Six months of IPT independently reduced the risk of severe HIV morbidity by 35% (3.0 vs. 4.7 severe events per 100 person years with IPT and no IPT, respectively; $P = .005$) with no overall increased risk of other adverse events. In the START study, 4,685 participants with CD4 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 initiation group and 20% of participants in the deferred initiation group.[9] 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 HIV/TB coinfection.

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

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 individuals without HIV. The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (Adult and Adolescent OI Guidelines)[10] include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include:

- When to start ART;
- Significant PK drug-drug interactions between anti-TB and ARV agents;
- The additive toxicities associated with concomitant ARV and anti-TB drug use; and
- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Tuberculosis Diagnosed While Patient is Receiving Antiretroviral Therapy

When TB is diagnosed in a patient receiving ART, the ARV regimen should be assessed with particular attention to potential PK 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 18a through 18e for dosing recommendations).

Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

In patients not taking ART at the time of TB diagnosis, delaying ART initiation for an extended period may

result in further immune decline with increased risk of new opportunistic diseases and death, especially in patients with advanced HIV disease. Several randomized controlled trials have attempted to address the optimal timing of ART initiation in the setting of active TB disease. The results of these trials have caused a paradigm shift favoring earlier ART initiation in patients with TB. The timing of ART in specific patient populations is discussed below.

Patients with CD4 count <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.[11-14] In these studies, early ART was defined as starting ART within 2 weeks and at no later than 4 weeks after initiation of TB therapy. In all three studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these three trials support initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm^3 **(AI)**.

Patients with CD4 counts ≥50 cells/mm^3: In the three studies mentioned above, there was no survival benefit for patients with CD4 count ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8 to 12 weeks) after beginning TB treatment. ART should not be delayed until TB treatment is completed, as this strategy was associated with higher mortality in the SAPiT-1 study.[11] Importantly, none of the studies demonstrated harm from earlier ART initiation, and there are many well-documented benefits from ART in people with HIV 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 over 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 the Panel recommends ART initiation within 8 weeks of starting TB treatment for those with ≥50 cells/mm^3 **(AIII)**.

Patients with drug-resistant TB: Mortality rates in patients with multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB and HIV are very high.[15] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such patients,[16,17] but the optimal timing for initiation of ART is unknown. Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged **(BIII)**.

Patients with TB meningitis: TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, patients were randomized to immediate ART or to ART deferred 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 with deferred therapy (80.3% vs. 69.1% for early and deferred ART, respectively; $P = 0.04$).[18] Therefore, caution should be exercised when initiating ART early in patients with TB meningitis **(AI)**.

Pregnant patients: All pregnant women with HIV and active TB should be started on ART as early as feasible, both for treatment of maternal HIV infection and to prevent perinatal transmission of HIV **(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).[19]

Drug Interaction Considerations

Rifamycins are a crucial component of TB treatment regimens. However, they are associated with a considerable potential for PK drug interactions. Rifampin is a potent inducer of the hepatic CYP 450 (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes. Rifabutin and rifapentine are CYP 3A4 substrates and inducers. As potent enzyme inducers, the rifamycins can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected by CYP induction include all protease inhibitors (PIs), non-nucleoside reverse

transcriptase inhibitors (NNRTIs), the integrase strand transfer inhibitors (INSTIs) elvitegravir (EVG) and the CCR5 antagonist maraviroc (MVC). Additionally, UGT1A1 induction may hasten the metabolism of the INSTIs dolutegravir (DTG) and RAL. Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and the fusion inhibitor enfuvirtide are not expected to have significant drug interactions with the rifamycins. As a P-gp substrate, tenofovir alafenamide (TAF)'s drug exposure may be reduced by rifamycins; therefore, concomitant administration of TAF and a rifamycin is not recommended at this time.[20] Tables 18a through 18e outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly.

As a potent enzyme inducer, rifampin use leads to significant reduction in ARV drug exposure; therefore, use of rifampin is not recommended for patients receiving PIs (boosted or unboosted), EVG, etravirine (ETR), rilpivirine (RPV), or TAF. Increased ARV doses are needed when rifampin is used with DTG, RAL, or MVC. In contrast to its effect on other ARV drugs, rifampin only leads to modest reduction in EFV concentrations.[21,22] Several observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of EFV.[23,24] Even though the current EFV label recommends increasing the EFV dose from 600 mg to 800 mg once daily in patients weighing >50 kg,[25] this dosage increase is generally not necessary.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 18a through 18e for dosing recommendations).

Rifapentine is a long-acting rifamycin which can be given once weekly with INH to treat latent TB infection.[26] Once-daily rifapentine is a more potent inducer than daily rifampin therapy.[27] The impact of once weekly dosing of rifapentine on the PKs of most ARV drugs has not been systematically explored. Once-daily rifapentine did not affect the oral clearance of EFV in individuals with HIV[28] and has minimal impact on EFV exposure when given once weekly,[6] whereas once-weekly rifapentine led to increase instead of decrease in RAL drug exposure in healthy volunteers.[7] Pending additional PK data on the effect of rifapentine on other ARV drugs, once-weekly INH plus rifapentine for LTBI treatment should only be given to patients receiving either an EFV- or RAL- based regimen **(AIII)**.

After selecting the ARV drugs and rifamycin to use, clinicians should determine the appropriate dose of each, and should closely monitor the patients to assure good control of both TB and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, adequacy of drug exposure (consider therapeutic drug monitoring [TDM]), or presence of acquired HIV or TB drug resistance.

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

IRIS is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections such as TB, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). TB-associated IRIS (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.[29,30] 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 a less than 30-day interval between initiation of TB and HIV treatments.[24,31-33] Most IRIS in HIV/TB disease occurs within 3 months of the start of ART.

Manifestations of unmasking 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.

IRIS ranges from mild to severe to life-threatening. Patients with mild or moderately severe IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. Patients with more severe IRIS can be treated successfully with corticosteroids, although data on the optimal dose, duration of therapy, and overall safety and efficacy are limited.[34] In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

References

1. World Health Organization. *Global Tuberculosis Report 2015*. 2015. Available at http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1.
2. Lawn SD, Harries AD, Williams BG, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *Int J Tuberc Lung Dis*. May 2011;15(5):571-581. Available at http://www.ncbi.nlm.nih.gov/pubmed/21756508.
3. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at http://www.ncbi.nlm.nih.gov/pubmed/20091503.
4. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of Mycobacterium tuberculosis infection in HIV co-infected persons. *AIDS*. Mar 17 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/26990624.
5. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. Jul 7 2011;365(1):11-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/21732833.
6. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine Once-Weekly Dosing Effect on Efavirenz Emtricitabine and Tenofovir PKs. 21st Conference on Retroviruses and Opportunistic Infections; 2014; Boston, MA.
7. Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. Apr 2014;69(4):1079-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/24343893.
8. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.
9. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med*. Aug 27 2015;373(9):795-807. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.
10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the *HIV Med*icine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed June 22, 2016.
11. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25 2010;362(8):697-706. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20181971.
12. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. Oct 20 2011;365(16):1492-1501. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010915.
13. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1471-1481. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010913.
14. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1482-1491. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010914.
15. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. Jan 1 2010;181(1):80-86. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19833824.

16. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet*. May 22 2010;375(9728):1798-1807. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20488525.
17. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. Apr 5 2014;383(9924):1230-1239. Available at http://www.ncbi.nlm.nih.gov/pubmed/24439237.
18. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. *Clin Infect Dis*. Jun 2011;52(11):1374-1383. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21596680.
19. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
20. Gilead Sciences. *Descovy Product Label*. Foster City, CA. 2016. Available at http://www.gilead.com/~/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf?la=en.
21. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41(9):681-690. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12126459.
22. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. Aug 2013;57(4):586-593. Available at http://www.ncbi.nlm.nih.gov/pubmed/23592830.
23. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother*. Dec 2006;58(6):1299-1302. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17032686.
24. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS*. Jan 2 2006;20(1):131-132. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327334.
25. Bristol-Myers Squibb. *Sustiva Product Label*. 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021360s024lbl.pdf.
26. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. Dec 9 2011;60(48):1650-1653. Available at http://www.ncbi.nlm.nih.gov/pubmed/22157884.
27. Dooley KE, Bliven-Sizemore EE, Weiner M, et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. *Clin Pharmacol Ther*. May 2012;91(5):881-888. Available at http://www.ncbi.nlm.nih.gov/pubmed/22472995.
28. Podany AT, Bao Y, Swindells S, et al. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. *Clin Infect Dis*. Oct 15 2015;61(8):1322-1327. Available at http://www.ncbi.nlm.nih.gov/pubmed/26082504.
29. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. Aug 2008;8(8):516-523. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18652998.
30. Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Jan 2 2010;24(1):103-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19926965.
31. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther*. 2005;10(3):417-422. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15918332.
32. Colebunders R, John L, Huyst V, Kambugu A, Scano F, Lynen L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis*. Sep 2006;10(9):946-953. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16964782.
33. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. Jan 30 2007;21(3):335-341. Available at http://

www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17255740.

34. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Sep 24 2010;24(15):2381-2390. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20808204.

Limitations to Treatment Safety and Efficacy

Adherence to the Continuum of Care (Last reviewed October 17, 2017)

Key Summary of Adherence to the Continuum of Care

- 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 initiation of ART and regularly thereafter.
- Patients with ART adherence problems should be placed on regimens with high genetic barriers to resistance, such as dolutegravir (DTG) or boosted darunavir (DRV). Side effects, out-of-pocket costs, convenience, and patient preferences also need to be considered.
- Patients having difficulties with adherence to appointments or ART should be approached in a constructive, collaborative, nonjudgmental, and problem-solving manner.
- The approach to improved adherence should be tailored to each person's needs (or barriers to care). Approaches could include, but are not limited to:
  - Changing ART to simplify dosing or reduce side effects
  - Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments
  - Allowing flexible appointment scheduling
  - Assisting with transportation, or
  - Linking patients to counseling to overcome stigma, substance use, or depression.
- Multidisciplinary approaches to find solutions to ART and appointment adherence problems are often necessary, including collaboration with 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 and reveal barriers to adherence, and link the patient to resources to overcome those barriers.
- A summary of best practice interventions to improve linkage, retention, and adherence can be found at a Centers for Disease Control and Prevention compendium (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html).

Introduction

Treatment adherence includes initiating care with an HIV provider (linkage to care), regularly attending appointments (retention in care), and adherence 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 treatment, retention in care, and virologic suppression.[1-3] The U.S. Centers for Disease Control and Prevention (CDC) estimates that HIV has not yet been diagnosed in about 13% of the people living with HIV in the United States. After receiving an HIV diagnosis, about 75% of individuals are linked to care within 30 days. However, only 57% of persons who receive an HIV diagnosis are retained in HIV care. It is estimated that only approximately 55% of persons with diagnosed HIV are virally suppressed because of poor linkage to care and retention in care.[4] The data for adolescents and young adults are even more sobering: only 51% of youth living with HIV receive a diagnosis, 68% are linked to care within 1 month, and 55% are retained in care. As a result, adolescents and young adults had the lowest rate of viral suppression among all age groups, at only 44%.[5] Outcomes along the continuum also vary by geographic region and other population characteristics, such as sex, race/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.

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

and evidence-informed interventions to improve linkage, retention, and adherence (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html). In addition, a number of other groups and organizations have provided guidance for improving adherence to the steps in the care continuum.[6,7]

Linkage to Care

Receiving a diagnosis of HIV infection can be traumatic and linkage to care efforts must be delivered with sensitivity 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).[8-12] 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-associated factors have also been associated with linkage success or failure. Co-location of testing and treatment services[11] and active linkage services (e.g., assisting the patient in setting up appointments, maintaining an active relationship with the patient until linkage is completed, and providing linkage case management services)[13-15] 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 persons 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 persons whose HIV is diagnosed outside the treatment provider's healthcare system is difficult and generally is the responsibility of the diagnosing provider/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 13. Linkage efforts should include immediate referral to care at diagnosis, appointment reminders, and outreach efforts if needed.[13] 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.[14] ARTAS is a strength-based intervention which aims to facilitate linkage to and retention in care for persons with recently diagnosed HIV. The ARTAS intervention was tested in four cities and enrolled a diverse group of persons. 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 Med*ical 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 the participant to identify and use his or her strengths, abilities, and skills to link to HIV care, and linked the participant 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 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, $P = 0.006$). ARTAS has been replicated in a community-based study.[15] CDC supports free training in the ARTAS intervention (https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/PublicHealthStrategies/ARTAS.aspx). Other studies support the importance of post-test counseling to educate, motivate, and present positive messages about

living with HIV,[16] peer support,[17] and engaging with the patient at the clinic in advance of the visit with the provider.[18] Financial incentives did not increase linkage to care within 90 days in a large randomized trial.[19]

Retention in Care

Poor retention in HIV care is associated with greater risk of death.[20,21] Poor retention is more common in persons who are substance users, have serious mental health problems, have unmet socioeconomic needs (e.g., housing, food, or transportation), lack financial resources or health insurance, have schedules that complicate adherence, have been recently incarcerated, or face stigma.[22-25] 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.[26-28] 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.[29] Both approaches are valid and independently predict survival.[30] Missed visits and a prolonged time since 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 13. The Retention through Enhanced Personal Contact (REPC) intervention was tested in a randomized trial in six clinics in the United States. The 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 clinic visit and three types of phone calls: to check on patients between visits, as 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 persons with detectable plasma HIV RNA.[31] In-clinic opioid replacement therapy helps opioid users remain in care.[32] 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.[33] On the other hand, in two randomized trials involving out-of-care, hospitalized patients with HIV, peer counselors and patient navigators did not improve relinkage to care after hospital discharge.[34,35] Data from nonrandomized studies support:

- 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,[36]
- Stepped case management and social and outreach services,[37] and
- "Data to Care" approaches which use clinic and public health data to reach out-of-care persons and re-engage them into care (see https://effectiveinterventions.cdc.gov/en/highimpactprevention/publichealthstrategies/DatatoCare.aspx).[38-40] However, the effectiveness of "data to care" interventions is variable and privacy concerns must be adequately addressed.

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 non-attendance, and collaboratively problem solving with patients to overcome barriers to care.[27,31,36] Flexible appointment schedules, expanded clinic hours, and copay and other financial or insurance assistance such as that provided by the Ryan White program will also provide patients with uninterrupted access to clinical care. Guidelines regarding linkage

and retention have been published.[6,7] CDC maintains a compendium of evidence-based and evidence-informed interventions (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html).

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%.[19] 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.[34] The use of financial incentives therefore remains experimental and cannot be recommended for 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.[41] Poor adherence is often a consequence of one or more behavioral, structural, and psychosocial barriers (e.g., depression and other mental illnesses, neurocognitive impairment, low health literacy, low levels of social support, stressful life events, busy or unstructured daily routines, active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, and inconsistent access to medications due to financial and insurance status).[42-44]

Characteristics of one or more components of the prescribed regimen can affect adherence. Once-daily regimens,[45] 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.[46,47] Single-tablet regimens (STR) that include all antiretrovirals in one pill taken once daily are easier for people to use. However, data to support or refute the superiority of a STR versus a once-daily multi-tablet regimen (MTR), as might be required for the use of some soon-to-be-available generic-based antiretroviral (ARV) regimens, are limited. There are demonstrated beneficial effects on virologic suppression in switch studies, in which persons on MTR are randomized to stay on MTR or switch to STR.[48] Whether an STR is beneficial in treatment-naive patients is not known, with at least one large observational cohort study showing benefit of once-daily STR versus once-daily MTR, but only when switches for simplification of MTR were considered failures.[47,49] Comparisons of these regimens are hampered since not all drugs and classes are available as STR.

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, and mental health and substance abuse providers) support patients' complex needs, including their medication adherence-related needs. Drug abuse treatment programs are often best suited to address substance use and 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 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.[50,51] 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.[52,53]

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 (e.g., Medication Event Monitoring System [MEMS] bottle caps and dispensing systems). However, these methods are costly and are generally reserved for research settings.

Improving Adherence to Antiretroviral Therapy

Strategies to improve adherence to ART are summarized in Table 13. Just as they support retention in care, all health care team members play integral roles in successful ART adherence programs.[51,54-56] An increasing number of interventions have proven effective in improving adherence to ART (for descriptions of the interventions, see http://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html). The many options can be customized to suit a range of needs and settings.

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 to 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 support staff, and can be accomplished concomitant with, or even after, starting therapy.[57-60] 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 in counseling 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.[57-60] For more details, see Initiation of Antiretroviral Therapy.

The first principle of successful treatment is to design a plan to which the patient can commit.[61,62] 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 and food requirements). With the patient's input, a medication choice and administration schedule should be tailored to his or her daily activities. Clinicians should explain to patients that their first regimen is usually the best option for a simple regimen that 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. There is strongest evidence for text messaging, but pill box monitors, pill boxes, and alarms may also improve adherence.[63-67]

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.[68-70] 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.[71] Problem-solving approaches that vary in intensity and culturally tailored approaches also are promising.[70,72,73] To maintain high levels of adherence in some patients, it is important to provide substance abuse therapy and to strengthen social support. DOT has been effective in providing ART to active drug users[74] but not to patients in a general clinic population[75] or in home-based settings with partners responsible for DOT.[76] The use of incentives or rewards to promote adherence has been studied, and they have been shown to improve adherence in one study.[19] However, the durability and feasibility of financial incentives are not known at this time, hence rewards for adherence are not generally recommended.[34,77,78]

Conclusion

Even armed with accurate information about a patient's adherence and barriers to ART and appointment adherence, clinicians often fail to engage patients in a productive conversation and instead simply tell patients to be adherent and offer warnings about what might ensue with continued poor adherence. This 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.[79,80] 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 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 13) 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 dolutegravir or boosted-darunavir regimens. When selecting the regimen, consider possible side effects, out-of-pocket costs, convenience, and patient preferences since 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 reveal any barriers to adherence, and link the patient to resources to overcome those barriers.

Table 13. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 1 of 2)

Strategies	Examples
Provide an accessible, trustworthy, nonjudgmental multidisciplinary health care team.	• Care providers, nurses, social workers, case managers, pharmacists, and medication managers.
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).
Evaluate 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 before starting ART and on an ongoing basis.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges, including depression, mental illnesses, 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, transportation problems.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage (e.g., Common Patient Assistance Program Application (CPAPA): http://bit.ly/CommonPAPForm; Pharmaceutical Company HIV Patient Assistance Programs and Cost-Sharing Assistance Programs: http://bit.ly/1XIahvN • Provide resources about stable housing, social support, transportation assistance, and income and food security.
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 ART if poor adherence is anticipated. • Consider use of STR formulations. • Assess if cost/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 low or nondetectable levels of HIV viral load and increases in CD4 cell counts. • Thank patients for attending their appointments.

Table 13. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 2 of 2)

Strategies	Examples
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. • Patient is unaware of appointments or appointments are not scheduled with proper patient input. • Cost-related issues (copays for medications or visits, missed work time). • Depression, drug and alcohol use, homelessness, poverty. • Stigma of taking pills or attending HIV-related appointments. • Nondisclosure of status leading to missed doses, refills, or appointments.
Select from among available effective adherence and retention interventions.	• See https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html 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). • Use patient prescription assistance programs (see above, 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 in persons in substance use treatment (if feasible). • Enhance clinic support and structures to promote linkage and retention (reminder calls, flexible scheduling, open access, active referrals, and improved patient satisfaction).
Systematically monitor retention in care.	• Record and follow up on missed visits.

Key to Acronyms: ART = antiretroviral therapy; ARTAS = Anti-Retroviral Treatment and Access to Services; ARV = antiretroviral; CD4 = CD4 T lymphocyte; DOT = directly observed therapy; DTG = dolutegravir; PI/r = ritonavir-boosted protease inhibitor; STR = single tablet regimen

References

1. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. Mar 15 2011;52(6):793-800. Available at https://www.ncbi.nlm.nih.gov/pubmed/21367734.

2. Greenberg AE, Hader SL, Masur H, Young AT, Skillicorn J, Dieffenbach CW. Fighting HIV/AIDS in Washington, D.C. *Health Aff*. Nov-Dec 2009;28(6):1677-1687. Available at https://www.ncbi.nlm.nih.gov/pubmed/19887408.

3. Giordano TP, Suarez-Almazor ME, Grimes RM. The population effectiveness of highly active antiretroviral therapy: are good drugs good enough? *Curr HIV/AIDS Rep*. Nov 2005;2(4):177-183. Available at https://www.ncbi.nlm.nih.gov/pubmed/16343375.

4. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2014. *HIV Surveillance Supplemental Report*. 2016;21(No. 4). Available at https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-

vol-21-4.pdf.

5. Centers for Disease Control and Prevention. *HIV Among Youth*. Division of HIV/AIDS Prevention; April 2017. Available at https://www.cdc.gov/hiv/pdf/group/age/youth/cdc-hiv-youth.pdf. Accessed August 15, 2017.

6. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med*. Jun 5 2012;156(11):817-833, W-284, W-285, W-286, W-287, W-288, W-289, W-290, W-291, W-292, W-293, W-294. Available at http://www.ncbi.nlm.nih.gov/pubmed/22393036.

7. International Advisory Panel on HIV Care Continuum Optimization. IAPAC guidelines for optimizing the HIV care continuum for adults and adolescents. *J Int Assoc Provid AIDS Care*. Nov-Dec 2015;14(Suppl 1):S3-S34. Available at https://www.ncbi.nlm.nih.gov/pubmed/26527218.

8. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. *PLoS Med*. Jul 2011;8(7):e1001056. Available at https://www.ncbi.nlm.nih.gov/pubmed/21811403.

9. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. *AIDS*. Oct 23 2012;26(16):2059-2067. Available at https://www.ncbi.nlm.nih.gov/pubmed/22781227.

10. Gardner LI, Marks G, Strathdee SA, et al. Faster entry into HIV care among HIV-infected drug users who had been in drug-use treatment programs. *Drug Alcohol Depend*. Aug 01 2016;165:15-21. Available at https://www.ncbi.nlm.nih.gov/pubmed/27296978.

11. Torian LV, Wiewel EW, Liu KL, Sackoff JE, Frieden TR. Risk factors for delayed initiation of medical care after diagnosis of human immunodeficiency virus. *Arch Intern Med*. Jun 09 2008;168(11):1181-1187. Available at https://www.ncbi.nlm.nih.gov/pubmed/18541826.

12. Giordano TP, Visnegarwala F, White AC Jr, et al. Patients referred to an urban HIV clinic frequently fail to establish care: factors predicting failure. *AIDS Care*. Aug 2005;17(6):773-783. Available at https://www.ncbi.nlm.nih.gov/pubmed/16036264.

13. Hightow-Weidman LB, Jones K, Wohl AR, et al. Early linkage and retention in care: findings from the outreach, linkage, and retention in care initiative among young men of color who have sex with men. *AIDS Patient Care STDS*. Aug 2011;25 Suppl 1:S31-38. Available at https://www.ncbi.nlm.nih.gov/pubmed/21711141.

14. Gardner LI, Metsch LR, Anderson-Mahoney P, et al. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. *AIDS*. Mar 04 2005;19(4):423-431. Available at https://www.ncbi.nlm.nih.gov/pubmed/15750396.

15. Craw JA, Gardner LI, Marks G, et al. Brief strengths-based case management promotes entry into *HIV Med*ical care: results of the antiretroviral treatment access study-II. *J Acquir Immune Defic Syndr*. Apr 15 2008;47(5):597-606. Available at https://www.ncbi.nlm.nih.gov/pubmed/18285714.

16. Muhamadi L, Tumwesigye NM, Kadobera D, et al. A single-blind randomized controlled trial to evaluate the effect of extended counseling on uptake of pre-antiretroviral care in Eastern Uganda. *Trials*. Jul 27 2011;12:184. Available at https://www.ncbi.nlm.nih.gov/pubmed/21794162.

17. Chang LW, Nakigozi G, Billioux VG, et al. Effectiveness of peer support on care engagement and preventive care intervention utilization among pre-antiretroviral therapy, HIV-infected adults in Rakai, Uganda: a randomized trial. *AIDS Behav*. Oct 2015;19(10):1742-1751. Available at https://www.ncbi.nlm.nih.gov/pubmed/26271815.

18. Mugavero MJ. Improving engagement in HIV care: what can we do? *Top HIV Med*. Dec 2008;16(5):156-161. Available at https://www.ncbi.nlm.nih.gov/pubmed/19106431.

19. El-Sadr WM, Donnell D, Beauchamp G, et al. Financial incentives for linkage to care and viral suppression among HIV-positive patients: a randomized clinical trial (HPTN 065). *JAMA Intern Med*. Aug 01 2017;177(8):1083-1092. Available at https://www.ncbi.nlm.nih.gov/pubmed/28628702.

20. Giordano TP, Gifford AL, White AC, Jr., et al. Retention in care: a challenge to survival with HIV infection. *Clin Infect Dis*. Jun 01 2007;44(11):1493-1499. Available at https://www.ncbi.nlm.nih.gov/pubmed/17479948.

21. Mugavero MJ, Lin HY, Willig JH, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. *Clin Infect Dis*. Jan 15 2009;48(2):248-256. Available at https://www.ncbi.nlm.nih.gov/pubmed/19072715.

22. Giordano TP, Hartman C, Gifford AL, Backus LI, Morgan RO. Predictors of retention in HIV care among a national cohort of US veterans. *HIV Clin Trials*. Sep-Oct 2009;10(5):299-305. Available at https://www.ncbi.nlm.nih.gov/pubmed/19906622.

23. Yehia BR, Stewart L, Momplaisir F, et al. Barriers and facilitators to patient retention in HIV care. *BMC Infect Dis*. Jun 28 2015;15:246. Available at https://www.ncbi.nlm.nih.gov/pubmed/26123158.

24. Bulsara SM, Wainberg ML, Newton-John TR. Predictors of adult retention in HIV care: a systematic review. *AIDS Behav*. Dec 19 2016. Available at https://www.ncbi.nlm.nih.gov/pubmed/27990582.

25. Doshi RK, Milberg J, Isenberg D, et al. High rates of retention and viral suppression in the US HIV safety net system: HIV care continuum in the Ryan White HIV/AIDS Program, 2011. *Clin Infect Dis*. Jan 01 2015;60(1):117-125. Available at https://www.ncbi.nlm.nih.gov/pubmed/25225233.

26. Flickinger TE, Saha S, Moore RD, Beach MC. Higher quality communication and relationships are associated with improved patient engagement in HIV care. *J Acquir Immune Defic Syndr*. Jul 01 2013;63(3):362-366. Available at https://www.ncbi.nlm.nih.gov/pubmed/23591637.

27. Dang BN, Westbrook RA, Hartman CM, Giordano TP. Retaining HIV patients in care: the role of initial patient care experiences. *AIDS Behav*. Oct 2016;20(10):2477-2487. Available at https://www.ncbi.nlm.nih.gov/pubmed/26910339.

28. Magnus M, Herwehe J, Murtaza-Rossini M, et al. Linking and retaining HIV patients in care: the importance of provider attitudes and behaviors. *AIDS Patient Care STDS*. May 2013;27(5):297-303. Available at https://www.ncbi.nlm.nih.gov/pubmed/23651107.

29. Mugavero MJ, Davila JA, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. *AIDS Patient Care STDS*. Oct 2010;24(10):607-613. Available at http://www.ncbi.nlm.nih.gov/pubmed/20858055.

30. Mugavero MJ, Westfall AO, Zinski A, et al. Measuring retention in HIV care: the elusive gold standard. *J Acquir Immune Defic Syndr*. Dec 15 2012;61(5):574-580. Available at https://www.ncbi.nlm.nih.gov/pubmed/23011397.

31. Gardner LI, Giordano TP, Marks G, et al. Enhanced personal contact with HIV patients improves retention in primary care: a randomized trial in 6 US HIV clinics. *Clin Infect Dis*. Sep 01 2014;59(5):725-734. Available at https://www.ncbi.nlm.nih.gov/pubmed/24837481.

32. Lucas GM, Chaudhry A, Hsu J, et al. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial. *Ann Intern Med*. Jun 01 2010;152(11):704-711. Available at https://www.ncbi.nlm.nih.gov/pubmed/20513828.

33. Robbins GK, Lester W, Johnson KL, et al. Efficacy of a clinical decision-support system in an HIV practice: a randomized trial. *Ann Intern Med*. Dec 04 2012;157(11):757-766. Available at https://www.ncbi.nlm.nih.gov/pubmed/23208165.

34. Metsch LR, Feaster DJ, Gooden L, et al. Effect of patient navigation with or without financial incentives on viral suppression among hospitalized patients with HIV infection and substance use: a randomized clinical trial. *JAMA*. Jul 12 2016;316(2):156-170. Available at https://www.ncbi.nlm.nih.gov/pubmed/27404184.

35. Giordano TP, Cully J, Amico KR, et al. A randomized trial to test a peer mentor intervention to improve outcomes in persons hospitalized with HIV infection. *Clin Infect Dis*. Sep 01 2016;63(5):678-686. Available at https://www.ncbi.nlm.nih.gov/pubmed/27217266.

36. Gardner LI, Marks G, Craw JA, et al. A low-effort, clinic-wide intervention improves attendance for HIV primary care. *Clin Infect Dis*. Oct 2012;55(8):1124-1134. Available at https://www.ncbi.nlm.nih.gov/pubmed/22828593.

37. Irvine MK, Chamberlin SA, Robbins RS, et al. Improvements in HIV care engagement and viral load suppression following enrollment in a comprehensive HIV care coordination program. *Clin Infect Dis*. Jan 15 2015;60(2):298-310. Available at https://www.ncbi.nlm.nih.gov/pubmed/25301208.

38. Bove JM, Golden MR, Dhanireddy S, Harrington RD, Dombrowski JC. Outcomes of a clinic-based surveillance-informed intervention to relink patients to HIV care. *J Acquir Immune Defic Syndr*. Nov 01 2015;70(3):262-268. Available at https://www.ncbi.nlm.nih.gov/pubmed/26068720.

39. Sena AC, Donovan J, Swygard H, et al. The North Carolina HIV Bridge Counselor Program: outcomes from a statewide

level intervention to link and reengage HIV-infected persons in care in the South. *J Acquir Immune Defic Syndr*. Sep 01 2017;76(1):e7-e14. Available at https://www.ncbi.nlm.nih.gov/pubmed/28394820.

40. Udeagu CC, Webster TR, Bocour A, Michel P, Shepard CW. Lost or just not following up: public health effort to re-engage HIV-infected persons lost to follow-up into *HIV Med*ical care. *AIDS*. Sep 10 2013;27(14):2271-2279. Available at https://www.ncbi.nlm.nih.gov/pubmed/23669157.

41. Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med*. Nov 2004;19(11):1096-1103. Available at http://www.ncbi.nlm.nih.gov/pubmed/15566438.

42. Halkitis PN, Shrem MT, Zade DD, Wilton L. The physical, emotional and interpersonal impact of HAART: exploring the realities of HIV seropositive individuals on combination therapy. *J Health Psychol*. May 2005;10(3):345-358. Available at http://www.ncbi.nlm.nih.gov/pubmed/15857867.

43. Stirratt MJ, Remien RH, Smith A, et al. The role of HIV serostatus disclosure in antiretroviral medication adherence. *AIDS Behav*. Sep 2006;10(5):483-493. Available at http://www.ncbi.nlm.nih.gov/pubmed/16721505.

44. Carr RL, Gramling LF. Stigma: a health barrier for women with HIV/AIDS. *J Assoc Nurses AIDS Care*. Sep-Oct 2004;15(5):30-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/15358923.

45. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis*. Feb 15 2009;48(4):484-488. Available at http://www.ncbi.nlm.nih.gov/pubmed/19140758.

46. Raboud J, Li M, Walmsley S, et al. Once daily dosing improves adherence to antiretroviral therapy. *AIDS Behav*. Oct 2011;15(7):1397-1409. Available at http://www.ncbi.nlm.nih.gov/pubmed/20878227.

47. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clin Infect Dis*. May 2014;58(9):1297-1307. Available at https://www.ncbi.nlm.nih.gov/pubmed/24457345.

48. Clay PG, Nag S, Graham CM, Narayanan S. Meta-analysis of studies comparing single and multi-tablet fixed dose combination HIV treatment regimens. *Medicine*. Oct 2015;94(42):e1677. Available at https://www.ncbi.nlm.nih.gov/pubmed/26496277.

49. Cotte L, Ferry T, Pugliese P, et al. Effectiveness and tolerance of single tablet versus once daily multiple tablet regimens as first-line antiretroviral therapy – Results from a large French multicenter cohort study. *PLoS One*. 2017;12(2):e0170661. Available at https://www.ncbi.nlm.nih.gov/pubmed/28152047.

50. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav*. May 2006;10(3):227-245. Available at https://www.ncbi.nlm.nih.gov/pubmed/16783535.

51. Mannheimer SB, Morse E, Matts JP, et al. Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. *J Acquir Immune Defic Syndr*. Dec 1 2006;43 Suppl 1:S41-47. Available at http://www.ncbi.nlm.nih.gov/pubmed/17091022.

52. Feldman BJ, Fredericksen RJ, Crane PK, et al. Evaluation of the single-item self-rating adherence scale for use in routine clinical care of people living with HIV. *AIDS Behav*. Jan 2013;17(1):307-318. Available at http://www.ncbi.nlm.nih.gov/pubmed/23108721.

53. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported *HIV Med*ication adherence. *AIDS Behav*. Jan 2008;12(1):86-94. Available at https://www.ncbi.nlm.nih.gov/pubmed/17577653.

54. McPherson-Baker S, Malow RM, Penedo F, Jones DL, Schneiderman N, Klimas NG. Enhancing adherence to combination antiretroviral therapy in non-adherent HIV-positive men. *AIDS Care*. Aug 2000;12(4):399-404. Available at http://www.ncbi.nlm.nih.gov/pubmed/11091772.

55. Kalichman SC, Cherry J, Cain D. Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS. *J Assoc Nurses AIDS Care*. Sep-Oct 2005;16(5):3-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/16433105.

56. Remien RH, Stirratt MJ, Dognin J, Day E, El-Bassel N, Warne P. Moving from theory to research to practice. Implementing an effective dyadic intervention to improve antiretroviral adherence for clinic patients. *J Acquir Immune*

Defic Syndr. Dec 1 2006;43 Suppl 1:S69-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/17133206.

57. Amanyire G, Semitala FC, Namusobya J, et al. Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial. *Lancet HIV*. Nov 2016;3(11):e539-e548. Available at https://www.ncbi.nlm.nih.gov/pubmed/27658873.

58. Rosen S, Maskew M, Fox MP, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: The RapIT randomized controlled trial. *PLoS Med*. May 2016;13(5):e1002015. Available at https://www.ncbi.nlm.nih.gov/pubmed/27163694.

59. Koenig S, Dorvil N, Severe P, et al. Same-day HIV testing and antiretroviral therapy initiation results in higher rates of treatment initiation and retention in care. *AIDS*; 2016; Durban, South Africa.

60. Pilcher CD, Ospina-Norvell C, Dasgupta A, et al. The effect of same-day observed initiation of antiretroviral therapy on HIV viral load and treatment outcomes in a US public health setting. *J Acquir Immune Defic Syndr*. Jan 01 2017;74(1):44-51. Available at https://www.ncbi.nlm.nih.gov/pubmed/27434707.

61. Williams A, Friedland G. Adherence, compliance, and HAART. *AIDS Clin Care*. 1997;9(7):51-54, 58. Available at https://www.ncbi.nlm.nih.gov/pubmed/11364415.

62. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. Oct 2001;26(5):331-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/11679023.

63. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS*. Mar 27 2011;25(6):825-834. Available at https://www.ncbi.nlm.nih.gov/pubmed/21252632.

64. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet*. Nov 27 2010;376(9755):1838-1845. Available at https://www.ncbi.nlm.nih.gov/pubmed/21071074.

65. Shet A, De Costa A, Kumarasamy N, et al. Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India. *BMJ*. Oct 24 2014;349:g5978. Available at https://www.ncbi.nlm.nih.gov/pubmed/25742320.

66. Sabin LL, Bachman DeSilva M, Gill CJ, et al. Improving Adherence to Antiretroviral Therapy With Triggered Real-time Text Message Reminders: The China Adherence Through Technology Study. *J Acquir Immune Defic Syndr*. Aug 15 2015;69(5):551-559. Available at https://www.ncbi.nlm.nih.gov/pubmed/25886927.

67. Petersen ML, Wang Y, van der Laan MJ, Guzman D, Riley E, Bangsberg DR. Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis. *Clin Infect Dis*. Oct 01 2007;45(7):908-915. Available at https://www.ncbi.nlm.nih.gov/pubmed/17806060.

68. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve *HIV Med*ication adherence among hazardous drinkers: a randomized controlled trial. *J Acquir Immune Defic Syndr*. Dec 01 2007;46(4):443-450. Available at https://www.ncbi.nlm.nih.gov/pubmed/18077833.

69. Gwadz M, Cleland CM, Applegate E, et al. Behavioral intervention improves treatment outcomes among HIV-infected individuals who have delayed, declined, or discontinued antiretroviral therapy: a randomized controlled trial of a novel intervention. *AIDS Behav*. Oct 2015;19(10):1801-1817. Available at https://www.ncbi.nlm.nih.gov/pubmed/25835462.

70. Bogart LM, Mutchler MG, McDavitt B, et al. A randomized controlled trial of rise, a community-based culturally congruent adherence intervention for black Americans living with HIV. *Ann Behav Med*. Apr 21 2017. Available at https://www.ncbi.nlm.nih.gov/pubmed/28432578.

71. Kanters S, Park JJ, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV*. Jan 2017;4(1):e31-e40. Available at https://www.ncbi.nlm.nih.gov/pubmed/27863996.

72. Gross R, Bellamy SL, Chapman J, et al. Managed problem solving for antiretroviral therapy adherence: a randomized trial. *JAMA Intern Med*. Feb 25 2013;173(4):300-306. Available at https://www.ncbi.nlm.nih.gov/pubmed/23358784.

73. de Bruin M, Oberje EJM, Viechtbauer W, et al. Effectiveness and cost-effectiveness of a nurse-delivered intervention to

improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial. *Lancet Infect Dis*. Jun 2017;17(6):595-604. Available at https://www.ncbi.nlm.nih.gov/pubmed/28262598.

74. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis*. Sep 15 2007;45(6):770-778. Available at https://www.ncbi.nlm.nih.gov/pubmed/17712763.

75. Berg KM, Litwin AH, Li X, Heo M, Arnsten JH. Lack of sustained improvement in adherence or viral load following a directly observed antiretroviral therapy intervention. *Clin Infect Dis*. Nov 2011;53(9):936-943. Available at http://www.ncbi.nlm.nih.gov/pubmed/21890753.

76. Gross R, Zheng L, La Rosa A, et al. Partner-based adherence intervention for second-line antiretroviral therapy (ACTG A5234): a multinational randomised trial. *Lancet HIV*. Jan 2015;2(1):e12-19. Available at https://www.ncbi.nlm.nih.gov/pubmed/26424232.

77. Galarraga O, Genberg BL, Martin RA, Barton Laws M, Wilson IB. Conditional economic incentives to improve HIV treatment adherence: literature review and theoretical considerations. *AIDS Behav*. Sep 2013;17(7):2283-2292. Available at https://www.ncbi.nlm.nih.gov/pubmed/23370833.

78. Bassett IV, Wilson D, Taaffe J, Freedberg KA. Financial incentives to improve progression through the HIV treatment cascade. *Curr Opin HIV AIDS*. Nov 2015;10(6):451-463. Available at https://www.ncbi.nlm.nih.gov/pubmed/26371461.

79. Wilson IB, Laws MB, Safren SA, et al. Provider-focused intervention increases adherence-related dialogue but does not improve antiretroviral therapy adherence in persons with HIV. *J Acquir Immune Defic Syndr*. Mar 2010;53(3):338-347. Available at https://www.ncbi.nlm.nih.gov/pubmed/20048680.

80. Laws MB, Beach MC, Lee Y, et al. Provider-patient adherence dialogue in HIV care: results of a multisite study. *AIDS Behav*. Jan 2013;17(1):148-159. Available at https://www.ncbi.nlm.nih.gov/pubmed/22290609.

Adverse Effects of Antiretroviral Agents (Last updated October 17, 2017; last reviewed October 17, 2017)

The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects of some antiretroviral (ARV) drugs. However, adverse effects have been reported with the use of all ARV drugs and, in the earlier era of combination ART, adverse effects were among the most common reasons for switching or discontinuing therapy and for medication nonadherence.[1] Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, less than 10% of ART-naive patients enrolled in randomized trials have treatment-limiting adverse events. However, the long-term complications of ART can be underestimated, because most clinical trials use highly specific inclusion criteria when enrolling participants and the duration of participant follow-up is relatively short. As ART is now recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy has to 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 such as bone or renal toxicity, dyslipidemia, insulin resistance, or accelerated cardiovascular disease. To achieve sustained viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and overcome. The clinician must consider potential adverse effects when selecting an ARV regimen, as well as the individual patient'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 or exacerbate adverse effects (e.g., alcoholism or coinfection with viral hepatitis[2,3] may increase the risk of hepatotoxicity; psychiatric disorders may be exacerbated by efavirenz [EFV], rilpivirine [RPV], and, infrequently, by integrase strand transfer inhibitors [INSTIs];[4,5] and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate [TDF])
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,[6,7] EFV neuropsychiatric toxicity and QTc prolongation,[8,9] and atazanavir (ATV)-associated hyperbilirubinemia.[10]

Information on the adverse effects of ARVs is outlined in several tables in the guidelines. Table 14 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 1–6.

Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 1 of 5

N/A indicates either that there are no reported cases for that particular side effect or that data for the specific ARV drug class are not available. See Appendix B for additional information listed by drug.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia **TPV:** Intracranial hemorrhage is associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, and vitamin E.	N/A	N/A
Bone Density Effects	**TDF:** Associated with greater loss of BMD than other NRTIs. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. **TAF:** Smaller declines in BMD than 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	**SQV/r, ATV/r, and LPV/r:** PR prolongation. Risk factors include pre-existing heart disease and other medications. **SQV/r:** QT prolongation. Obtain ECG before administering SQV.	N/A	N/A
Cardiovascular Disease	**ABC and ddI:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	**DRV, FPV, IDV, 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.	N/A	N/A

Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 2 of 5

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Diabetes Mellitus and Insulin Resistance	**ZDV, d4T, and ddI**	N/A	Reported for some (IDV, LPV/r), but not all, PIs.	N/A	N/A
Dyslipidemia	**d4T > ZDV > ABC:** ↑ TG and LDL **TAF:** ↑ TG, ↑ LDL, ↑ 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 and FPV/r > DRV/r and ATV/r:** ↑ TG	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	N/A
Gastrointestinal Effects	**ddI and ZDV > other NRTIs:** Nausea and vomiting **ddI:** Pancreatitis	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) **NFV and LPV/r > DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	N/A
Hepatic Effects	**Reported with most NRTIs.** **ZDV, d4T, or ddI:** Steatosis **ddI:** Prolonged exposure linked to noncirrhotic portal hypertension and esophageal varices. **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.	**EFV:** Fulminant hepatitis progressing to hepatic failure requiring transplantation or death have been reported. **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. Two-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency occurs with TPV/r. **TPV/r: Contraindicated** in patients with hepatic insufficiency (Child Pugh class B or C). **IDV, ATV:** Jaundice due to indirect hyperbilirubinemia.	N/A	**MVC:** Hepatotoxicity with or without rash or HSRs reported.

Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 3 of 5

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC: Contraindicated** if HLA-B*5701-positive. Median onset for HSR is 9 days; 90% of reactions occur within first 6 weeks of treatment. **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 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. Overall, risk is higher for women than men. Two-week dose escalation of NVP reduces risk.	N/A	**RAL:** HSR reported when RAL is given with other drugs also known to cause HSR. 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.
Lactic Acidosis	**Reported with NRTIs, especially d4T, ZDV, and ddI:** Insidious onset with GI prodrome, weight loss, and fatigue. May rapidly progress with tachycardia, tachypnea, jaundice, weakness, mental status changes, pancreatitis, and organ failure. Mortality high if serum lactate >10 mmol/L. Women and obese patients at increased risk.	N/A	N/A	N/A	N/A

Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 4 of 5

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Lipodystrophy	**Lipoatrophy: d4T > ZDV.** More likely when NRTIs are coadministered with EFV than with an RTV-boosted PI.	**Lipohypertophy:** 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, DTG:** ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A
Nervous System/ Psychiatric Effects	**d4T > ddI:** Peripheral neuropathy (can be irreversible) **d4T:** Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare).	**EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2 to 4 weeks. Bedtime dosing may reduce symptoms. Risk factors include presence of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide was found in a retrospective analysis of comparative trials. **RPV:** Depression, suicidality, sleep disturbances	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, FPV, LPV/r, TPV**	**All INSTIs**	**MVC**

Table 14. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy, page 5 of 5

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:** Increased risk of chronic kidney disease in a large cohort study. **IDV:** ↑ SCr, pyuria, renal atrophy, or hydronephrosis **IDV, 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 and COBI (as a boosting agent for EVG):** Inhibits Cr secretion without reducing renal glomerular function.	N/A
Stevens-Johnson Syndrome/ Toxic Epidermal Necrosis	Some reported cases for **ddI and ZDV**.	**NVP > DLV, EFV, ETR, RPV**	Some reported cases for **FPV, DRV, IDV, LPV/r, and ATV.**	**RAL**	N/A

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; Cr = creatinine; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IDV = indinavir; 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; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Switching Antiretroviral Therapy Because of 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 additional pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching from an effective ARV regimen (or agent) to a new regimen (or agent) must be done carefully and only when the potential benefits of the change outweigh the potential complications 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 resistance mutations, regardless of when the mutations were identified by genotypic resistance testing, are archived in HIV reservoirs. Even if resistance mutations are absent from subsequent resistance test results, they may reappear under selective drug pressure. 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 resistance test results;
- Viral tropism (if maraviroc [MVC] is being considered);
- HLA-B*5701 status (if ABC is being considered);
- Comorbidities;
- Adherence history;
- Prior intolerances to any ARVs; and
- Concomitant medications and supplements, taking into consideration any potential drug interactions with ARVs.

A patient's willingness to accept new food or dosing requirements 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 those of 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 viral load should also be monitored to assure continued viral suppression.

Table 15 lists several major ART-associated adverse events and potential options to appropriately switch 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 a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	ABC[b] or TAF 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	TDF, TAF, or ABC[b]	ZDV has been associated with neutropenia and macrocytic anemia.
Cardiac QTc Interval Prolongation	EFV, RPV	A PI- or INSTI-based regimen	High EFV and RPV 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.
Cardiovascular Events Myocardial infarction, ischemic stroke	ABC	TDF, TAF, FTC, 3TC	ABC use has been associated with cardiovascular 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, EVG/c	RAL, DTG, RPV	RAL, DTG, and RPV have less effect on lipids. 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.
Central Nervous System, Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV, RPV	ETR or a PI/c or PI/r INSTIs may be considered with monitoring (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. 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.
Dyslipidemia Hyper-triglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted regimens, EFV, EVG/c	RAL, DTG, 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]

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, EVG/c	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 substitution unless persistent and intolerable.
	Other RTV- or COBI-boosted regimens	RAL, DTG, NNRTIs	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	TDF or TAF	Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.
	NVP, EFV, ETR, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 cell 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, FPV/r	INSTI, RPV	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than 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 Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF, TAF, or ABC[b]	Peripheral lipoatrophy is a legacy of prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow (may take years) and incomplete.
Lipohypertrophy	Accumulation of visceral, truncal, dorso-cervical, 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 weight or visceral fat gain.		
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen	Mild rashes developing 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 with close follow-up only. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.

Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 3 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Renal Effects Including proximal renal tubulopathy and elevated creatinine	TDF[a]	ABC,[b] or TAF (for patients with CrCl >30 mL/min), 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	DTG, RAL, or NNRTI	COBI and DTG, 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.
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Assuming that ATV is believed to be causing the stones.

[a] In patients with chronic active HBV infection, another agent 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. Long-term data for unboosted ATV are unavailable.

Key to Abbreviations: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; 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; 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; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

References

1. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr*. 2003;34(4):407-414. Available at https://www.ncbi.nlm.nih.gov/pubmed/14615659.
2. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. Dec 22 2000;14(18):2895-2902. Available at https://www.ncbi.nlm.nih.gov/pubmed/11153671.
3. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. *Antimicrob Agents Chemother*. Dec 2000;44(12):3451-3455. Available at https://www.ncbi.nlm.nih.gov/pubmed/11083658.
4. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. Sep 12 2008;22(14):1890-1892. Available at https://www.ncbi.nlm.nih.gov/pubmed/18753871.
5. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. Aug 24 2015;29(13):1723-1725. Available at http://www.ncbi.nlm.nih.gov/pubmed/26372287.

6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. Feb 7 2008;358(6):568-579. Available at https://www.ncbi.nlm.nih.gov/pubmed/18256392.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. Apr 1 2008;46(7):1111-1118. Available at https://www.ncbi.nlm.nih.gov/pubmed/18444831.
8. Gounden V, van Niekerk C, Snyman T, George JA. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther*. 2010;7:32. Available at http://www.ncbi.nlm.nih.gov/pubmed/20723261.
9. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6*6*6 allele carriers. *J Cardiovasc Electrophysiol*. Oct 2016;27(10):1206-1213. Available at https://www.ncbi.nlm.nih.gov/pubmed/27333947.
10. Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. *AIDS*. Jan 2 2007;21(1):41-46. Available at http://www.ncbi.nlm.nih.gov/pubmed/17148966.

Cost Considerations and Antiretroviral Therapy (Last updated July 14, 2016; last reviewed July 14, 2016)

Although antiretroviral therapy (ART) is expensive (see Table 16 below), the cost-effectiveness of ART has been demonstrated in analyses of older[1] and newer regimens,[2,3] as well as for treatment-experienced patients with drug-resistant HIV.[4] Given the recommendations for immediate initiation of lifelong treatment and the increasing number of patients taking ART, the Panel now introduces cost-related issues pertaining to medication adherence and cost-containment strategies, as discussed below.

Costs as They Relate to Adherence from a Patient Perspective

Cost sharing: Cost sharing is where the patient is responsible for some of the medication cost burden (usually accomplished via copayments, coinsurance, or deductibles); these costs are often higher for branded medications than for generic medications. In one comprehensive review, increased patient cost sharing resulted in decreased medical adherence and more frequent drug discontinuation; for patients with chronic diseases, increased cost sharing was also associated with increased use of the medical system.[5] Conversely, copayment reductions, such as those that might be used to incentivize prescribing of generic drugs, have been associated with improved adherence in patients with chronic diseases.[6] Whereas cost sharing disproportionately affects low-income patients, resources (e.g., the Ryan White AIDS Drug Assistance Program [ADAP]) are available to assist eligible patients with copays and deductibles. Given the clear association between out-of-pocket costs for patients with chronic diseases and the ability of those patients to pay for and adhere to medications, clinicians should minimize patients' out-of-pocket drug-related expenses whenever possible.

Prior authorizations: As a cost-containment strategy, some programs require that clinicians obtain prior authorizations or permission before prescribing newer or more costly treatments rather than older or less expensive drugs. Although there are data demonstrating that prior authorizations do reduce spending, several studies have also shown that prior authorizations result in fewer prescriptions filled and increased nonadherence.[7-9] Prior authorizations in HIV care specifically have been reported to cost over $40 each in provider personnel time (a hidden cost) and have substantially reduced timely access to medications.[10]

Generic ART: The impact of the availability of generic antiretroviral (ARV) drugs on selection of ART in the United States is unknown. Because U.S. patent laws currently limit the coformulation of some generic alternatives to branded drugs, generic options may result in increased pill burden. 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.[11,12] Furthermore, prescribing the individual, less-expensive generic components of a branded coformulated product rather than the branded product itself could, under some insurance plans, lead to higher copays—an out-of-pocket cost increase that may reduce medication adherence.

Potential Cost Containment Strategies from a Societal Perspective

Given resource constraints, it is important to maximize the use of resources without sacrificing clinical outcomes. Evidence-based revisions to these guidelines recommend tailored laboratory monitoring for patients with long-term virologic suppression on ART as one possible way to provide overall cost savings. Data suggest that continued CD4 monitoring yields no clinical benefit for patients whose viral loads are suppressed and whose CD4 counts exceed 200 cells/mm^3 after 48 weeks of therapy.[13] A reduction in laboratory use from biannual to annual CD4 monitoring could save ~$10 million per year in the United States[14] (see Laboratory Monitoring). Although this is a small proportion of the overall costs associated with HIV care, such a strategy could reduce patients' personal expenses if they have deductibles for laboratory tests. The present and future availability of generic formulations of certain ARV drugs, despite the potential caveats of increased pill burden and reduced adherence, offers other money-saving possibilities on a much

greater scale. One analysis suggests the possibility of saving approximately $900 million nationally in the first year of switching from a branded fixed-dose combination product to a three-pill regimen containing generic efavirenz.[3]

In summary, understanding HIV and ART related-costs in the United States is complicated because of the wide variability in medical coverage, accessibility, and expenses across regions, insurance plans, and pharmacies. In an effort to retain excellent clinical outcomes in an environment of cost-containment strategies, providers should remain informed of current insurance and payment structures, ART costs (see Table 16 below for estimates of drugs' average wholesale prices), discounts among preferred pharmacies, and available generic ART options. Providers should work with patients and their case managers and social workers to understand their patients' particular pharmacy benefit plans and potential financial barriers to filling their prescriptions. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company patient assistance programs for patients who qualify) and refer patients to such assistance if needed.

Table 16. Monthly Average Wholesale Price[a] of Commonly Used[b] Antiretroviral Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 3)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Dosing	Tablets, Capsules, or mLs per Month[c]	AWP[a] (Monthly)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir				
• Generic	300 mg tablet	2 tablets daily	60 tablets	$502.22–$603.33
• Ziagen	300 mg tablet	2 tablets daily	60 tablets	$670.37
• Ziagen	20 mg/mL solution	30 mL daily	900 mL	$660.86
Emtricitabine				
• Emtriva	200 mg capsules	1 cap daily	30 capsules	$643.82
• Emtriva	10 mg/mL solution	24 mL daily	680 mL (28-day supply)	$608.16
Lamivudine				
• Generic	300 mg tablet	1 tablet daily	30 tablets	$324.33–$429.66
• Epivir	300 mg tablet	1 tablet daily	30 tablets	$498.89
• Epivir	10 mg/mL solution	30 mL daily	900 mL	$498.90
Tenofovir Disoproxil Fumarate				
• Viread	300 mg tablet	1 tablet daily	30 tablets	$1,279.94
Zidovudine				
• Generic	300 mg tablet	1 tablet twice daily	60 tablets	$54.00–$365.44
NRTI Combination Products				
Abacavir/Lamivudine				
• Generic	600/300 mg tablets	1 tablet daily	30 tablets	$1,395.00
• Epzicom	600/300 mg tablets	1 tablet daily	30 tablets	$1,550.05
Tenofovir Alafenamide/Emtricitabine				
• Descovy	25/200 mg tablet	1 tablet daily	30 tablets	$1,881.14
Tenofovir Disoproxil Fumarate/ Emtricitabine				
• Truvada	300/200 mg tablet	1 tablet daily	30 tablets	$1,881.14
Zidovudine/Lamivudine				
• Generic	300/150 mg tablet	1 tablet twice daily	60 tablets	$877.85–$931.61
• Combivir	300/150 mg tablet	1 tablet twice daily	60 tablets	$1,081.70
Abacavir Sulfate/Zidovudine/Lamivudine				
• Generic	300/300/150 mg tablet	1 tablet twice daily	60 tablets	$1,738.46
• Trizivir	300/300/150 mg tablet	1 tablet twice daily	60 tablets	$1,931.64

Table 16. Monthly Average Wholesale Price[a] of Commonly Used[b] Antiretroviral Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 3)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Dosing	Tablets, Capsules, or mLs per Month[c]	AWP[a] (Monthly)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz • Sustiva	600 mg tablet	1 tablet daily	30 tablets	$1,176.74
Etravirine • Intelence	200 mg tablet	1 tablet twice daily	60 tablets	$1,411.42
Nevirapine • Generic	200 mg tablet	1 tablet twice daily	60 tablets	$648.19–$650.70
• Viramune	200 mg tablet	1 tablet twice daily	60 tablets	$967.63
• Viramune XR	400 mg tablet	1 tablet daily	30 tablets	$897.46
Rilpivirine • Edurant	25 mg tablet	1 tablet daily	30 tablets	$1,160.10
Protease Inhibitors (PIs)				
Atazanavir • Reyataz	200 mg capsule	2 capsules daily	60 capsule	$1,755.91
• Reyataz	300 mg capsule[d]	1 capsule daily	30 capsule	$1,739.50
Atazanavir/Cobicistat • Evotaz	300/150 mg tablet	1 tablet daily	30 tablets	$1,926.56
Darunavir • Prezista	600 mg tablet[e]	1 tablet twice daily	60 tablets	$1,757.77
• Prezista	800 mg tablet[d]	1 tablet daily	30 tablets	$1,757.77
• Prezista	100 mg/mL suspension[e]	8 mL daily 6 mL twice daily	240 mL 360 mL	$1,171.85 $1,757.77
Darunavir/Cobicistat • Prezcobix	800/150 mg tablet	1 tablet daily	30 tabs	$2,009.23
Lopinavir/Ritonavir • Kaletra	200/50 mg tablet	2 tablets twice daily or 4 tablets once daily	120 tablets	$1,160.50
• Kaletra	80/20 mg per mL solution	5 mL twice daily	300 mL	$1,087.97
Tipranavir • Aptivus	250 mg capsule[e]	2 capsules twice daily	120 capsules	$1,786.73
Integrase Strand Transfer Inhibitors (INSTIs)				
Dolutegravir • Tivicay	50 mg tablet	1 tablet once daily	30 tablets	$1,842.82
• Tivicay	50 mg tablet	1 tablet twice daily	60 tablets	$3,685.64
Raltegravir • Isentress	400 mg tablet	1 tablet twice daily	60 tablets	$1,667.52
• Isentress HD	600 mg tablet	2 tablets once daily	60 tablets	$1,667.52
Fusion Inhibitor				
Enfuviritide • Fuzeon	90 mg injection kit	1 injection twice daily	60 doses (1 kit)	$4,302.67
CCR5 Antagonist				
Maraviroc • Selzentry	150 mg tablet	1 tablet twice daily	60 tablets	$1,679.68
• Selzentry	300 mg tablet	1 tablet twice daily	60 tablets	$1,679.68
• Selzentry	300 mg tablet	2 tablets twice daily	120 tablets	$3,359.36

Table 16. Monthly Average Wholesale Price[a] of Commonly Used[b] Antiretroviral Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 3)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Dosing	Tablets, Capsules, or mLs per Month[c]	AWP[a] (Monthly)
Coformulated Combination Products as Single Tablet Regimens				
Dolutegravir/Abacavir/Lamivudine • Triumeq	50/600/300 mg tablet	1 tablet daily	30 tablets	$3,118.62
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine • Atripla	600/300/200 mg tablet	1 tablet daily	30 tablets	$3,057.89
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine • Genvoya	150/150/10/200 mg tablet	1 tablet daily	30 tablets	$3,306.92
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine • Stribild	150/150/300/200 mg tablet	1 tablet daily	30 tablets	$3,707.99
Rilpivirine/Tenofovir Alafenamide/ Emtricitabine • Odefsey	25/25/200 mg tablet	1 tablet daily	30 tablets	$3,009.29
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine • Complera	25/300/200 mg tablet	1 tablet daily	30 tablets	$3,216.92
Pharmacokinetic Enhancers (Boosters)				
Cobicistat • Tybost	150 mg tablet	1 tablet daily	30 tablets	$246.84
Ritonavir: Total daily dose depends on the dose of the concomitant PI (100 mg once or twice daily, or 200 mg twice daily)				
• Norvir	100 mg tablet	1 tablet once daily	30 tablets	$308.60
• Norvir	80 mg/mL solution	100 mg daily	37.5 mL (of a 240 mL bottle)	$270.04

[a] AWP = average wholesale price. Note that the AWP may not represent the pharmacy acquisition price or the price paid by public and private payors or consumers. Source: http://www.micromedexsolutions.com. Accessed September 2017.

[b] The following less commonly used ARV drugs are not included in this table: delavirdine, didanosine, fosamprenavir, indinavir, nelfinavir, saquinavir, and stavudine.

[c] Represents 30 days or as specified.

[d] Should be used in combination with ritonavir or cobicistat. Please refer to Appendix B, Table 3 for ritonavir doses.

[e] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

Key to Acronyms: ARV = antiretroviral; XR = extended release

References

1. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. Mar 15 2001;344(11):824-831. Available at https://www.ncbi.nlm.nih.gov/pubmed/11248160.

2. Mauskopf J, Brogan AJ, Talbird SE, Martin S. Cost-effectiveness of combination therapy with etravirine in treatment-experienced adults with HIV-1 infection. *AIDS*. Jan 28 2012;26(3):355-364. Available at http://www.ncbi.nlm.nih.gov/pubmed/22089378.

3. Walensky RP, Sax PE, Nakamura YM, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med*. Jan 15 2013;158(2):84-92. Available at http://www.ncbi.nlm.nih.gov/pubmed/23318310.

4. Bayoumi AM, Barnett PG, Joyce VR, et al. Cost-effectiveness of newer antiretroviral drugs in treatment-experienced patients with multidrug-resistant HIV disease. *J Acquir Immune Defic Syndr*. Dec 1 2013;64(4):382-391. Available at http://www.ncbi.nlm.nih.gov/pubmed/24129369.

5. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA*. Jul 4 2007;298(1):61-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/17609491.

6. Maciejewski ML, Farley JF, Parker J, Wansink D. Copayment reductions generate greater medication adherence in targeted patients. *Health Aff*. Nov 2010;29(11):2002-2008. Available at http://www.ncbi.nlm.nih.gov/pubmed/21041739.

7. Abdelgawad T, Egbuonu-Davis L. Preferred drug lists and Medicaid prescriptions. *Pharmacoeconomics*. 2006;24 Suppl 3:55-63. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266388.

8. Ridley DB, Axelsen KJ. Impact of Medicaid preferred drug lists on therapeutic adherence. *Pharmacoeconomics*. 2006;24 Suppl 3:65-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266389.

9. Wilson J, Axelsen K, Tang S. Medicaid prescription drug access restrictions: exploring the effect on patient persistence with hypertension medications. *Am J Manag Care*. Jan 2005;11 Spec No:SP27-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/15700907.

10. Raper JL, Willig JH, Lin HY, et al. Uncompensated medical provider costs associated with prior authorization for prescription medications in an HIV clinic. *Clin Infect Dis*. Sep 15 2010;51(6):718-724. Available at http://www.ncbi.nlm.nih.gov/pubmed/20695800.

11. Hanna DB, Hessol NA, Golub ET, et al. Increase in Single-Tablet Regimen Use and Associated Improvements in Adherence-Related Outcomes in Hiv-Infected Women. *J Acquir Immune Defic Syndr*. Dec 8 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/24326606.

12. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clin Infect Dis*. May 2014;58(9):1297-1307. Available at https://www.ncbi.nlm.nih.gov/pubmed/24457345.

13. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS*. Nov 13 2013;27(17):2759-2763. Available at http://www.ncbi.nlm.nih.gov/pubmed/23842127.

14. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med*. Oct 14 2013;173(18):1746-1748. Available at http://www.ncbi.nlm.nih.gov/pubmed/23978894.

Drug-Drug Interactions (Last updated October 17, 2017; last reviewed October 17, 2017)

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 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 other drugs a patient is taking. 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 particular 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 are prescribed concomitantly. When prescribing interacting drugs is necessary, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common mechanisms of interactions are described below and listed for each ARV drug in Table 17.

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 ARVs that require gastric acidity for optimal absorption (i.e., atazanavir [ATV] and rilpivirine [RPV]).
- Products that contain polyvalent cations, such as aluminum, calcium, magnesium-containing antacids, supplements, or iron products, can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme cytochrome P450 3A4 (CYP3A4) 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 cytochrome P450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), the CCR5 antagonist maraviroc (MVC), and the INSTI elvitegravir (EVG). CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARVs 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 dolutegravir (DTG) and raltegravir (RAL). Drugs that induce or inhibit the UGT enzyme can affect 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 of these drugs are potent inhibitors of the CYP3A4 enzyme, resulting in higher systemic exposures of the coadministered ARV metabolized by this pathway. 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, phenytoin, voriconazole, oral contraceptives, and certain HMG-CoA reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

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.

Tables 18a through 19b 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 modifications or alternative therapy.

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 1 of 2)

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. 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 CYP- and UGT1A1-mediated interactions.

Note: Ellipses [...] indicates that there are no clinically relevant interactions by these mechanisms.

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				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
INSTIs								
DTG	...	Concentration decreased by products containing polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Substrate	3A4 (minor)	...	...	Substrate	Inhibitor of renal transporters OCT2 and MATE
EVG	...		...	3A4	...	2C9	Substrate	...
RAL	...		...	...	...	...	Substrate	...
PK Enhancers (Boosters)								
COBI	...	...	Inhibitor	3A4	3A4, 2D6	...	...	...
RTV	...	...	Substrate, inhibitor	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer	...
PIs **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
ATV	Concentration decreased	...	Substrate, inducer, inhibitor	3A4	3A4, 2C8 (weak)	...	Inhibitor	OATP inhibitor

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 2 of 2)

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				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
PIs, continued								
DRV	...	...	Substrate	3A4	3A4	2C9	...	OATP inhibitor
FPV	Concentration decreased by H2 antagonist	...	Substrate, inhibitor	3A4	3A4	3A4 (weak)	...	...
LPV	...	...	Substrate	3A4	3A4	...	...	OATP inhibitor
SQV	...	...	Substrate, inhibitor	3A4	3A4	...	...	OATP inhibitor
TPV	...	...	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	...	OATP inhibitor
NNRTIs								
EFV	...	...	...	2B6 (primary), 2A6, 3A4	2C9, 2C19, 3A4	3A4, 2B6	...	...
ETR	...	...	Inhibitor	3A4, 2C9, 2C19	2C9, 2C19	3A4	...	...
NVP	...	...	...	3A4, 2B6	...	3A4, 2B6	...	...
RPV	Concentration decreased	...	...	3A4	...	...	...	...
NRTIs								
ABC	...	...	...	...	...	...	Substrate	Alcohol dehydrogenase substrate
FTC	...	...	...	...	...	...	...	...
3TC	...	...	...	...	...	...	...	...
TAF	...	...	Substrate	...	...	...	...	OATP substrate
TDF	...	...	Substrate	...	...	...	...	Competition of active renal tubular secretion
ZDV	...	...	...	...	...	...	...	Glucuronidation
CCR5 Antagonist								
MVC	...	...	Substrate	3A4	...	...	...	...
Fusion Inhibitor								
T20	...	...	...	...	...	...	...	...

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; Ca = calcium; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; Fe = iron; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; OCT2 = organic cation transporter 2; OATP = organic anion-transporting polypeptide; PK = pharmacokinetic; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase; ZDV = zidovudine; Zn = zinc

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 17)

This table provides known or predicted information regarding PK interactions between PIs and non-ARV drugs. When information is available, interactions for specific PK-boosted (with either RTV or COBI) and unboosted ATV are listed separately. The term "All PIs" refers to both unboosted ATV and PIs boosted with either RTV or COBI, except the PIs noted below. For interactions between ARV agents and for dosing recommendations, refer to Tables 18c, 19a, and 19b.

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.

Note: Fosamprenavir (FPV), indinavir (IDV), nelfinavir (NFV), and saquinavir (SQV) are **not** included in this table. Please refer to the Food and Drug Administration product labels for FPV, IDV, NFV, and SQV for information regarding drug interactions with these PIs..

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	ATV (unboosted)	↓ ATV	H2 receptor antagonist single dose 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 BID in PI-naive patients. Unboosted ATV + famotidine should not be used in combination in PI-experienced patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	ATV/c, ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + COBI 150 mg or RTV 100 mg simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg + COBI 150 mg or RTV 100 mg.
	DRV/c, DRV/r, LPV/r	↔ demonstrated or expected	No dose adjustment necessary.
PPIs	ATV (unboosted)	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV or COBI boosting, or alternative PIs.
	ATV/c, ATV/r	↓ ATV	PPIs 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. **PPIs are not recommended in PI-experienced patients.**
	DRV/c, LPV/r	↔ expected	No dose adjustment necessary.
	DRV/r	Omeprazole AUC ↓ 42%	No dose adjustment necessary. If there is a lack of symptomatic relief, increase omeprazole dose to no more than 40 mg daily if needed.

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
PPIs, continued	TPV/r	Omeprazole AUC ↓ 70%	**Coadministration is not recommended.** If coadministration is necessary, dose increases of omeprazole may be considered based on clinical response.
Anticoagulants and Antiplatelets			
Apixaban	PI/c, PI/r	↑ apixaban expected	**Coadministration is not recommended.** Consider alternative ARV or warfarin. If coadministration is necessary, reduce apixaban dose by 50% and monitor for apixaban toxicity.
Betrixaban	PI/r	↑ or ↓ betrixaban possible	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
	ATV/c, DRV/c	↑ betrixaban expected	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
Dabigatran	PI/r	With RTV 100 mg + dabigatran taken simultaneously: ↔ dabigatran Dabigatran given 2 hours before RTV 100 mg: dabigatran AUC ↓ 29%	The extent of interaction of PI/r + dabigratran is unknown. Consider alternative ARV or warfarin. If coadministered, take dabigatran and PI/r simultaneously.
	ATV/c, DRV/c	With COBI 150 mg: dabigatran AUC ↑ 110%–127%	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
Edoxaban	PI/r	↑ or ↓ edoxaban possible	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
	ATV/c, DRV/c	↑ edoxaban expected	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
Rivaroxaban	PI/c, PI/r	↑ rivaroxaban expected	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
Ticagrelor	All PIs	↑ ticagrelor expected	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
Vorapaxar	All PIs	↑ vorapaxar expected	**Coadministration is not recommended.** Consider alternative ARV or warfarin.
Warfarin	PI/r	↓ warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly.
	ATV/c, DRV/c	No data	Monitor INR closely when stopping or starting PI/c 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.
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ARV.
	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
	ATV/r, LPV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Carbamazepine, continued	DRV/r	Carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
Oxcarbazepine, Eslicarbazepine	All PIs	↓ PI possible	Consider alternative anticonvulsant or ARV. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentration.
Ethosuximide	All PIs	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Lamotrigine	ATV (unboosted)	Lamotrigine: no effect	No dose adjustment necessary.
	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; consider monitoring lamotrigine concentration or consider alternative anticonvulsant.
	LPV/r	Lamotrigine AUC ↓ 50% LPV: no significant change	
	DRV/r, TPV/r	↓ lamotrigine possible	
	ATV/c, DRV/c	No data	Monitor lamotrigine concentration or consider alternative anticonvulsant.
Phenobarbital	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
	ATV (unboosted), PI/r	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily or unboosted ATV.**
Phenytoin	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ATV/r.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
	LPV/r	Phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Valproic Acid	PI/c, PI/r	↓ or ↔VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.
Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below)			
Bupropion	LPV/r	Bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	Bupropion AUC ↓ 46%	
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Lurasidone	PI/c, PI/r	↑ lurasidone expected	**Contraindicated.**
	ATV (unboosted)	↑ lurasidone expected	Consider alternative therapy. If coadministration is necessary, reduce lurasidone dose by 50%.

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below), continued			
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	RTV	Escitalopram ↔	Titrate SSRI dose based on clinical response.
	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	
	ATV/r, LPV/r, TPV/r	No data	
	ATV/c, DRV/c	Effects unknown	Titrate SSRI dose using the lowest available initial or maintenance dose.
Pimozide	All PIs	↑ pimozide expected	**Contraindicated.**
Quetiapine	All PIs	↑ quetiapine expected	Starting Quetiapine in a Patient Receiving a PI: Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. Starting a PI in a Patient Receiving a Stable Dose of Quetiapine: Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Other Antipsychotics (e.g., perphenazine, risperidone, thioridazine)	PI/c, PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Trazodone	All PIs	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and CV adverse effects.
Tricyclic Antidepressants Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	All PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Antifungals			
Fluconazole	PI/c, ATV/r, DRV/r, LPV/r	No significant effect observed or expected	No dose adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative ARV.
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%	If coadministered, consider monitoring isavuconazole concentrations and toxicities and assessing virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, consider monitoring isavuconazole concentrations and toxicities. Monitor for PI toxicity and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. Doses >200 mg/day are not recommended with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole levels.

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 5 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	ATV/r	ATV AUC ↑ 146% ↑ posaconazole possible	If coadministered, monitor for PI adverse effects. Consider monitoring posaconazole concentrations and toxicities.
	ATV	ATV AUC ↑ 268% ↑ posaconazole possible	
	ATV/c, DRV/c, DRV/r, LPV/r, TPV/r	↑ PI possible ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	All PI/r	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not coadminister voriconazole and RTV or COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentration and adjust dose accordingly.
	ATV/c, DRV/c	Effects unknown	
Antihyperglycemics			
Canagliflozin	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, has an eGFR >60 mL/min/1.73m^2, and requires additional glycemic control, consider increasing canagliflozin dose to 300 mg daily.
	PI/c	↓ canagliflozin possible	If used in combination, monitor glycemic control.
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily
Dapagliflozin/ Saxagliptin	All PIs	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
Antimalarials			
Artemether/ Lumefantrine	DRV/r	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
	DRV/c	↑ lumefantrine expected Effect on artemether unknown	
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 17% Lumefantrine AUC ↑ 470%	
Artesunate/ Mefloquine	LPV/r	Dihydroartemisinin AUC ↓ 49% Mefloquine AUC ↓ 28% LPV ↔	Clinical significance unknown. If used, monitor closely for antimalarial efficacy.

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 6 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials, continued			
Atovaquone/ Proguanil	ATV/r, LPV/r	With ATV/r: • ↓ atovaquone AUC 46% • ↓ proguanil AUC 41% With LPV/r: • ↓ atovaquone AUC 74% • ↓ proguanil AUC 38%	No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Mefloquine	RTV	With RTV 200 mg BID: • RTV AUC ↓ 31%, C_{min} ↓ 43% • ↔ mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections)			
Bedaquiline	All PIs	With LPV/r: • Bedaquiline AUC ↑ 1.9-fold With other PI/r, ATV/c, or DRV/c: • ↑ bedaquiline possible	Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests.
Clarithromycin	ATV (unboosted)	Clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	All PIs	↑ clarithromycin expected DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% TPV/r ↑ clarithromycin 19% Clarithromycin ↑ TPV 66%	Consider alternative macrolide (e.g., azithromycin). Monitor for clarithromycin-related toxicities or consider an alternative macrolide (e.g., azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30−60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week.
	ATV/c, DRV/c	↑ rifabutin expected	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in the healthy study participants.
	ATV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg once daily) + ATV/r: • rifabutin AUC ↑ 110% and metabolite AUC ↑ 2101%	
	DRV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) + DRV/r: • rifabutin AUC ↔ and metabolite AUC ↑ 881%	
	LPV/r	Compared with rifabutin (300 mg daily) alone, rifabutin (150 mg once daily) + LPV/r: • rifabutin and metabolite AUC ↑ 473%	

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 7 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections), continued			
Rifabutin, continued	TPV/r	Rifabutin and metabolite AUC ↑ 333%	
Rifampin	All PIs	↓ PI concentration by >75%	**Contraindicated.** Additional RTV does not overcome this interaction and may increase hepatotoxicity. Additional COBI is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone	ATV/r	Atovaquone ↔	No dose adjustment necessary.
Cardiac Medications			
Amiodarone	TPV/r	↑ both amiodarone and PI possible	**Contraindicated.**
	All PIs except TPV/r	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative antiarrhythmics or ARV. If coadministered, monitor for antiarrhythmic toxicities.
	PI/c, PI/r	↑ antiarrhythmic possible	**Do not coadminister.** Consider alternative antiarrhythmics or ARV.
Dronedarone	ATV (unboosted)	↑ dronedarone possible	**Do not coadminister.**
	PI/c, PI/r	↑ dronedarone expected	**Contraindicated.**
Flecanide	All PIs except TPV/r	↑ flecainide possible	**Do not coadminister.**
	TPV/r	↑ flecanide expected	**Contraindicated.**
Propafenone	All PIs except TPV/r	↑ propafenone possible	**Do not coadminister.**
	TPV/r	↑ propafenone expected	**Contraindicated.**
Quinidine	All PIs except TPV/r	↑ quinidine possible	**Do not coadminister.**
	TPV/r	↑ quinidine expected	**Contraindicated.**
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 CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (day 4) and 5-fold (day 10) ↓ 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 (CCBs), Except Diltiazem	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.
Digoxin	PI/r, PI/c	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41%, AUC ↔	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV/c, ATV/r, ATV (unboosted)	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/c, DRV/r, LPV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
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 BID ↑ 17-BMP AUC 2-fold	No dose adjustment necessary.
	All PIs except DRV/r	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-fold	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Consider an alternative corticosteroid (e.g., beclomethasone).

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic corticosteroid outweigh the risks of systemic corticosteroid adverse effects.**
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 systemic corticosteroid adverse effects. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-associated toxicities.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylpred-nisolone, 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.
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 necessary.
	TPV/r	No data	No dosing recommendations available at this time.
Dasabuvir + Paritaprevir/ Ombitasvir/RTV	ATV (unboosted)	ATV ↔	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir + paritaprevir/ombitasvir/RTV.
	DRV	DRV C_{min} ↓ 43% to 48%	**Do not coadminister.**
	LPV/r	Paritaprevir AUC ↑ 117%	**Do not coadminister.**
	ATV/c, DRV/c, TPV/r	No data	**Do not coadminister.**

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 10 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Elbasvir/ Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold ATV ↔ by elbasvir ATV AUC ↑ 43% by grazoprevir	**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, TPV/r	↑ grazoprevir expected	
Glecaprevir/ Pibrentasvir	ATV (unboosted), ATV/c, ATV/r	When Given with ATV/r 300/100 mg Once Daily: • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	**Contraindicated.**
	DRV/c, DRV/r	When Given with DRV/r 800/100 mg Once Daily: • Glecaprevir AUC ↑ 5-fold • ↔ pibrentasvir	**Do not coadminister.**
	LPV/r	↑ glecaprevir AUC 4-fold ↑ pibrentasvir 2.5-fold	**Do not coadminister.**
	TPV/r	↑ glecaprevir and pibrentasvir expected	**Do not coadminister.**
Ledipasvir/ Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose adjustment necessary. 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 TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions.
	DRV/r	DRV ↔ expected ↔ ledipasvir/sofosbuvir	
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ expected	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 11 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Simeprevir	All PIs	Compared with Simeprevir 150 mg Alone, Simeprevir 50 mg + DRV/r 800/100 mg Daily: • Simeprevir AUC ↑ 159% RTV 100 mg BID ↑ simeprevir AUC 618%	**Do not coadminister.**
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment necessary.
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓28% ↔ velpatasvir	No dose adjustment necessary.
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ sofosbuvir and velpatasvir expected	No dose adjustment necessary.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir/ Voxilaprevir	ATV (unboosted), ATV/c, ATV/r	When Given with ATV/r: • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	**Do not coadminister.**
	LPV/r	↑ voxilaprevir expected	**Do not coadminister.**
	DRV/r, DRV/c	When Given with DRV/r: • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected Effect on voxilaprevir is unknown	**Do not coadminister.**
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Contraindicated.**
Hormonal Therapies			
Hormonal Contraceptives Oral	ATV (unboosted)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or recommend alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.[c]

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 12 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Hormonal Contraceptives Oral	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[b] Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	ATV/c	Drospirenone AUC ↑ 2.3-fold Ethinyl estradiol AUC ↓ 22%	**Contraindicated with drosperinone-containing hormonal contraceptive. Do not coadminister due to potential for hyperkalemia.** Consider alternative or additional contraceptive method or alternative ARV drug.
	DRV/c	Drospirenone AUC ↑ 1.6-fold Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method or alternative ARV.
	DRV/r, LPV/r, TPV/r	Ethinyl estradiol AUC ↓ 37% to 55% Norethindrone AUC ↓ 14% to 34% With TPV/r: norethindrone AUC ↔	Consider alternative or additional contraceptive method or alternative ARV drug.
Depot Medroxy-progesterone Acetate (MPA) Injectable	LPV/r	MPA AUC ↑ 46% C_{min}: no significant change	No dose adjustment necessary.
Etonogestrel-Releasing Subdermal Implant	LPV/r	Etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.
Transdermal Ethinyl Estradiol/ Norelgestromin	LPV/r	LPV ↔ Ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.
Menopausal Hormone Replacement Therapy	All PIs	With estradiol or conjugated estrogen (equine and synthetic): ↓ estrogen possible	Adjust estrogen dosage as needed based on clinical effects.
	All PIs	↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See Hormonal Contraceptives for other progestin-PI interactions	Adjust progestin/progesterone dosage as needed based on clinical effects. Because drospirenone is prescribed as a lower dose for menopausal HRT than the products used for hormonal contraceptives, it is not contraindicated with ATV/c products.

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 13 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Gender-Affirming Hormone Therapy	All PIs	↓ estradiol possible	Adjust estradiol dosage as needed based on clinical effects and endogenous hormone concentrations.
	All PIs	↔ finasteride, goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment necessary.
	All PIs	↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	All PIs	↓ testosterone possible	Adjust testosterone dosage as needed based on clinical effects and endogenous hormone concentrations.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV, ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold, C_{max} ↑ 18.9-fold	**Coadministration is not recommended.**
	DRV/r	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Titrate atorvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	DRV/c	Atorvastatin AUC ↑ 3.9-fold, C_{max} ↑ 4.2-fold	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	LPV/r	Atorvastatin AUC ↑ 5.9-fold, C_{max} ↑ 4.7-fold	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	TPV/r	Atorvastatin AUC ↑ 9.4-fold, C_{max} ↑ 8.6-fold	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31%, C_{max} ↑ 60% ↔ ATV DRV/r ↓ pitavastatin AUC 26% ↔ DRV/r LPV/r ↓ pitavastatin AUC 20% ↔ LPV	No dose adjustment necessary.
Pravastatin	ATV/c, ATV/r	No data	Titrate pravastatin dose carefully while monitoring for toxicities.
	DRV/c, DRV/r	With DRV/r, Pravastatin AUC: • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Titrate pravastatin dose carefully while monitoring for toxicities.
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary.

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 14 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Rosuvastatin	ATV/r	Rosuvastatin AUC ↑ 3-fold, C_{max} ↑ 7-fold	Titrate rosuvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 10 mg rosuvastatin daily.
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold, C_{max} ↑ 10.6-fold	
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold, C_{max} ↑ 3.8-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities. Do not exceed 20 mg rosuvastatin daily.
	DRV/r	Rosuvastatin AUC ↑ 48%, C_{max} ↑ 2.4-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	LPV/r	Rosuvastatin AUC ↑ 2.1-fold, C_{max} ↑ 4.7-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	TPV/r	Rosuvastatin AUC ↑ 26%, C_{max} ↑ 2.2-fold	No dose adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin expected	**Contraindicated.**
Immunosuppressants			
Cyclosporine, Everolimus, 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 toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV (unboosted)	Buprenorphine AUC ↑ 93% Norbuprenorphine[d] AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.**
	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine[d] AUC ↑ 105%	Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	ATV/c, DRV/c	Effects unknown	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. Clinical monitoring is recommended.
	DRV/r	Buprenorphine: no significant effect Norbuprenorphine[d] AUC ↑ 46%, C_{min} ↑ 71%	No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	LPV/r	No significant effect	
	TPV/r	Buprenorphine: no significant effect Norbuprenorphine[d] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19%–40%	Consider monitoring TPV level. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 15 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence, continued			
Fentanyl	All PIs	↑ fentanyl possible	Clinical monitoring is recommended, including for potentially fatal respiratory depression.
Methadone	ATV (unboosted)	No significant effect	No dose adjustment necessary.
	ATV/c, DRV/c	Effects unknown	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended.
	All PI/r	ATV/r and DRV/r ↓ R-methadone[e] AUC 16%–18% LPV/r ↓ methadone AUC 26% to 53% TPV/r ↓ R-methadone[e] AUC 48%	Opioid withdrawal is unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Oxycodone	All PIs	Oxycodone AUC ↑ 2.6-fold with LPV/r	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Tramadol	ATV/c, DRV/c	↑ tramadol possible	Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Avanafil	All PIs except unboosted ATV	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold, C_{max} 2.4-fold	**Coadministration is not recommended.**
	ATV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
Sildenafil	All PIs	DRV/r + sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg BID ↑ sildenafil AUC 1000%	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For Treatment of PAH: • **Contraindicated.**
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% TPV/r steady state: no significant effect	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For Treatment of PAH: *In patients on a PI >7 days:* • Start with tadalafil 20 mg once daily and increase to 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 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 2.5 mg per day.

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 16 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phosphodiesterase Type 5 (PDE5) Inhibitors, continued			
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Alprazolam, Clonazepam, Diazepam	All PIs	↑ benzodiazepine possible RTV (200 mg BID 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; thus, there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Suvorexant	All PIs	↑ suvorexant expected	**Coadministration is not recommended.**
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000%	**Contraindicated.**
Zolpidem	PI/r, ATV/c, DRV/c	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.
Miscellaneous Drugs			
Alfuzosin	All PIs	↑ alfuzosin expected	**Contraindicated.**
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 BID ↑ colchicine AUC 296%, C_{max} 184% With all PIs with or without COBI or RTV: significant ↑ colchicine expected	For Treatment of Gout Flares: • Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares: • Colchicine 0.3 mg once daily or every other day. For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
Dronabinol	All PIs	↑ dronabinol possible	Monitor for increased dronabinol-related adverse reactions.
Eluxadoline	All PIs	↑ eluxadoline expected	Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse effects.
Ergot Derivatives	All PIs	↑ dihydroergotamine, ergotamine, methylergonovine expected	**Contraindicated.**

Table 18a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 17 of 17)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
Flibanserin	All PIs	↑ flibanserin expected	**Contraindicated.**
Irinotecan	ATV, ATV/c, ATV/r	↑ irinotecan expected	**Contraindicated.**
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated CV events.

[a] DHA is an active metabolite of artemether.

[b] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl.

[c] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): 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.

[d] Norbuprenorphine is an active metabolite of buprenorphine.

[e] R-methadone is the active form of methadone.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; COBI, c = 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; HCV = hepatitis C virus; HRT = hormone replacement therapy; INR = international normalized ratio; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MPA = medroxyprogesterone acetate; PAH = pulmonary arterial hypertension; 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, r = ritonavir; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; VPA = valproic acid

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 9)

This table provides information relating to PK interactions between NNRTIs and non-ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 18c, 19a, and 19b. 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.

Note: Delavirdine (DLV) is **not** included in this table. Please refer to the DLV Food and Drug Administration package insert for information regarding drug interactions.

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	RPV	↓ RPV	Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.
PPIs	RPV	With Omeprazole 20 mg Daily: • RPV AUC ↓ 40%, C_{min} ↓ 33%	**Contraindicated. Do not coadminister.**
Anticoagulants/Antiplatelets			
Apixaban	EFV, ETR, NVP	↓ apixaban possible	Consider alternative therapy.
Betrixaban	EFV, NVP, RPV	↔ betrixaban expected	No dose adjustment necessary.
	ETR	↑ betrixaban possible	Consider alternative therapy. If coadministration is necessary, reduce betrixaban initial dose to 80 mg, followed by 40 mg daily. Monitor for betrixaban toxicity.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
	NVP, RPV	↔ clopidogrel expected	No dose adjustment necessary.
Dabigatran	EFV, NVP, RPV	↔ dabigatran expected	No dose adjustment necessary.
	ETR	↑ dabigatran possible	Consider alternative therapy. If coadministration is necessary, monitor for dabigatran toxicity.
Edoxaban	EFV, NVP, RPV	↔ edoxaban expected	No dose adjustment necessary.
	ETR	↑ edoxaban possible	Consider alternative therapy. If coadministration is necessary, monitor for edoxaban toxicity.
Prasugrel	EFV, ETR, NVP, RPV	↔ prasugrel expected	No dose adjustment necessary.
Rivaroxaban	EFV, ETR, NVP	↓ rivaroxaban possible	Consider alternative therapy.
Ticagrelor	EFV, ETR, NVP	↓ ticagrelor expected	Consider alternative therapy.
Warfarin	EFV, ETR, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	EFV	Carbamazepine + EFV: • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% Phenytoin + EFV: • ↓ EFV • ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Eslicarbazepine	EFV, ETR, NVP, RPV	↓ NNRTI possible	Monitor virologic outcomes and consider monitoring plasma concentrations of ARVs, or consider alternative anticonvulsant or ARV drug.
Oxcarbazepine	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Ethosuximide, Lacosamide, Tiagabine, Zonisamide,	ETR, EFV	↓ anticonvulsant possible	Monitor seizure control and plasma concentrations of anticonvulsants (when available).
Lamotrigine	EFV	↓ lamotrigine possible	Monitor seizure control and plasma concentrations of lamotrigine.
Antidepressants			
Bupropion	EFV, NVP	Bupropion AUC ↓ 55% ↓ bupropion possible	Titrate bupropion dose based on clinical response.
Citalopram, Escitalopram	EFV, ETR, NVP	↓ antidepressant possible	Titrate antidepressant dose based on clinical response.
Fluoxetine, Fluvoxamine	EFV, ETR, NVP, RPV	↔ antidepressant expected	No dose adjustment necessary.
Paroxetine	EFV, ETR, NVP, RPV	↔ paroxetine observed with EFV or ETR ↔ expected with NVP or RPV	No dose adjustment necessary.
Nefazodone	EFV, ETR, NVP	↓ nefazodone expected ↑ NNRTI possible	Monitor the antidepressant effect and titrate dose as necessary. Monitor for ARV-related adverse events.
	RPV	↑ RPV possible	
Sertraline	EFV	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
Trazodone	EFV, ETR, NVP	↓ trazodone possible	Monitor the therapeutic effect of trazodone and titrate dose as necessary.

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	↔ fluconazole or EFV	No dose adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dose adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dose adjustment necessary.
Isavuconazole	EFV, ETR, NVP	↓ isavuconazole possible	Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole level and antifungal response.
	RPV	↑ RPV possible	No dose adjustment necessary.
Itraconazole	EFV	Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35%–44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	Itraconazole AUC ↓ 61% ↑ NVP possible	Avoid this combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↑ RPV possible	No dose adjustment necessary.
Posaconazole	EFV	Posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	ETR, NVP, RPV	↑ NNRTI possible	Monitor for NNRTI toxicities.
Voriconazole	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** Dose Adjustment: • Voriconazole 400 mg BID, EFV 300 mg daily
	ETR	Voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dose adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↑ RPV possible	No dose adjustment necessary.
Antihyperglycemics			
Canagliflozin, Dapagliflozin, Empagliflozin, Sitagliptin	EFV, ETR, NVP, RPV	↔ antihyperglycemic expected	No dose adjustment necessary.
Linagliptin, Saxagliptin	EFV, ETR, NVP	↓ antihyperglycemic possible	Monitor glycemic control.

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 4 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials			
Artemether/ Lumefantrine	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy and malaria recurrence.
	ETR	Artemether AUC ↓ 38% DHA AUC ↓ 15% Lumefantrine AUC ↓ 13% ETR AUC ↑ 10%	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor closely for antimalarial efficacy.
	NVP	Artemether AUC ↓ 67%–72% DHA: • Study results are conflicting. AUC ↓ 37% in one study, no difference in another. Lumefantrine: • Study results are conflicting. Lumefantrine AUC ↓ 25%– 58% in 2 studies but ↑ 56% in another.	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	EFV	Atovaquone AUC ↓ 75% Proguanil AUC ↓ 43%	No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials			
Bedaquiline	EFV, ETR	↓ bedaquiline possible	**Do not coadminister.**
	NVP	↔ bedaquiline AUC	No dose adjustment necessary.
Clarithromycin	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	Clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31% NVP AUC ↑ 26%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	Rifabutin ↓ 38%	Dose: • Rifabutin 450–600 mg/day; or • Rifabutin 600 mg 3 times/week if EFV is not coadministered with a PI.
	ETR	Rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: • Rifabutin 300 mg once daily if ETR is not coadministered with a PI/r.

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 5 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials			
Rifabutin, continued	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dose adjustment necessary. Use with caution.
	RPV	Rifabutin + RPV 50 mg once daily compared to RPV 25 mg once daily alone: ↔ RPV AUC, C_{min}	Increase RPV dose to 50 mg once daily.
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20%–58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated. Do not coadminister.**
Rifapentine	EFV	↔ EFV concentrations	No dose adjustment necessary.
	ETR, NVP	↓ NNRTI possible	**Do not coadminister.**
	RPV	↓ RPV expected	**Contradindicated.**
Antipneumocystis and Antitoxoplasmosis Drugs			
Atovaquone	EFV	Atovaquone AUC ↓ 44%–47%	Consider alternative agent for PCP or toxoplasmosis treatment or use alternative ARV drug. If used in combination, monitor therapeutic efficacy of atovaquone.
Antipsychotics			
Olanzapine	EFV	↓ olanzapine possible	Monitor effect of olanzapine.
	ETR, NVP, RPV	↔ olanzapine expected	No dose adjustment necessary.
Pimozide	EFV	↑ pimozide possible	**Coadministration is not recommended.** Consider alternative antipsychotic.
	ETR, NVP	↓ pimozide possible	Monitor effect of pimozide.
Lurasidone, Quetiapine, Thioridazine	EFV, ETR, NVP	↓ antipsychotic possible	Monitor effect of antipsychotic.
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	↓ alprazolam possible	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	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	EFV	Lorazepam C_{max} ↑ 16%, AUC ↔	No dose adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 6 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Dihydropyridine CCBs	EFV, ETR, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem, Verapamil	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, and NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	EFV, ETR, NVP	Daclatasvir 120 mg once daily + EFV 600 mg daily compared to daclatasvir 60 mg alone: daclatasvir C_{min} ↓ 17%, AUC ↑ 37%	The recommended dose is daclatasvir 90 mg once daily.
	RPV	No data	No dose adjustment necessary.
Dasabuvir + Paritaprevir/ Ombitasivir/RTV	EFV	No data	**Contraindicated.**
	ETR, NVP	↓ DAAs possible	**Do not coadminister.**
	RPV	RPV AUC ↑ 150%–225%	**Do not coadminister, due to potential for QT interval prolongation with higher concentrations of RPV.**
Elbasvir/ Grazoprevir	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓ 83% EFV ↔ by grazoprevir EFV ↔ AUC by elbasvir	**Contraindicated.**
	ETR, NVP	↓ elbasvir, grazoprevir expected	**Do not coadminister.**
	RPV	Elbasvir, grazoprevir, and RPV ↔	No dose adjustment necessary.
Glecaprevir/ Pibrentasvir	EFV	↓ glecaprevir and pibrentasvir expected	**Do not coadminister.**
	NVP, ETR	↓ glecaprevir and pibrentasvir possible	
	RPV	↔ glecaprevir, pibrentasvir, and RPV AUC ↑ 84%	No dose adjustment necessary.
Ledipasvir/ Sofosbuvir	EFV	Ledipasvir AUC, C_{min}, and C_{max}: all ↓ 34% Sofosbuvir: no significant effect	No dose adjustment necessary.
	ETR, NVP	No significant effect expected	
	RPV	Ledipasvir, sofosbuvir, and RPV ↔	

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 7 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Simeprevir	EFV	Simeprevir AUC ↓ 71%, C_{min} ↓ 91% ↔ EFV	**Do not coadminister.**
	ETR, NVP	↓ simeprevir expected	**Do not coadminister.**
	RPV	↔ simeprevir and RPV	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir	EFV	Velpatasvir AUC ↓ 43% , C_{max} ↓ 37% and C_{min} ↓ 47%	**Do not coadminister.**
	ETR, NVP	↓ velpatasvir expected	**Do not coadminister.**
	RPV	No significant effect expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir/ Voxilaprevir	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.**
	RPV	No signficant effect expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	EFV, ETR, NVP, RPV	↓ NNRTI	**Contraindicated.**
Hormonal Therapies			
Hormonal Contraceptives	EFV	Ethinyl estradiol ↔ Levonorgestrel (metabolite of oral norgestimate) AUC ↓ 83% Norelgestromin (metabolite of oral norgestimate) AUC ↓ 64% Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 61% Etonogestrel (implant) AUC ↓ 63%–82% Levonorgestrel (implant) AUC ↓ 47%	Use alternative or additional contraceptive methods. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.
		DMPA: no significant change	No dose adjustment necessary.
	ETR	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No dose adjustment necessary.
	NVP	Ethinyl estradiol AUC ↓ 29%, C_{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 22%	Based on clinical data demonstrating no change in effectiveness, no dose adjustment necessary.
		Etonogestrel (implant): no significant change	No dose adjustment necessary.
		DMPA: no significant change	No dose adjustment necessary.

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 8 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Hormonal Contraceptives, continued	NVP, continued	Levonorgestrel (implant) AUC ↑ 35%	No dose adjustment necessary.
	RPV	Ethinyl estradiol: no significant change Norethindrone: no significant change	No dose adjustment necessary.
Levonorgestrel For emergency contraception	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
Menopausal Hormone Replacement Therapy	EFV, ETR, NVP	With estradiol or conjugated estrogen (equine and synthetic): ↓ estrogen possible ↓ medroxyprogesterone possible ↓ micronized progesterone possible ↓ drospirenone possible See Hormonal Contraceptives for other progestin-NNRTI interactions	Monitor menopausal symptoms. The lowest dose of hormonal therapy should be used to achieve menopausal symptom relief.
Gender-Affirming Hormone Therapy	EFV, ETR, NVP	↓ estradiol possible ↔ goserelin, leuprolide acetate, and spironolactone expected ↓ dutasteride and finasteride possible	Monitor feminizing effects of estrogen and antiandrogen therapy and adjust dosing as necessary.
	EFV, ETR, NVP	↓ testosterone possible	Monitor masculinizing effects of testosterone and adjust testosterone dose as necessary.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	Atorvastatin AUC ↓ 32%–43%	Adjust atorvastatin according to lipid responses, but do not exceed the maximum recommended dose.
	NVP	↓ atorvastatin possible	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ↔ Atorvastatin metabolites ↑ 23%–39%	No dose adjustment necessary.
Fluvastatin	EFV, ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin, Simvastatin	EFV	Simvastatin AUC ↓ 68% Simvastatin active metabolite AUC ↓ 60%	Adjust simvastatin dose according to lipid responses, but do not exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, but do not exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided.

Table 18b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 9 of 9)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Pitavastatin	EFV	Pitavastatin AUC ↓ 11%, C_{max} ↑ 20%	No dose adjustment necessary.
	ETR, NVP, RPV	↔ pitavastatin expected	No dose adjustment necessary.
Pravastatin	EFV	AUC ↓ 44%	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
Rosuvastatin	EFV, ETR, NVP	↔ rosuvastatin expected	No dose adjustment necessary.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatments for Opioid Dependence			
Buprenorphine Sublingual or buccal	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine[b] AUC ↓ 71%	No dose adjustment recommended; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment necessary.
	NVP	No significant effect	No dose adjustment necessary.
Buprenorphine Implant	EFV, ETR, NVP	No data	Clinical monitoring is recommended if NNRTI is initiated after insertion of buprenorphine implant.
Methadone	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dose adjustment necessary.
	NVP	Methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dose adjustment necessary, but monitor for withdrawal symptoms.
PDE5 Inhibitors			
Sildenafil	ETR	Sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	EFV, NVP	↓ sildenafil possible	
	RPV	↔ sildenafil	No dose adjustment necessary.
Avanafil, Tadalafil, Vardenafil	EFV, ETR, NVP	↓ PDE5 inhibitor possible	May need to increase PDE5 inhibitor dose based on clinical effect.

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.
[b] Norbuprenorphine is an active metabolite of buprenorphine.
[c] R-methadone is the active form of methadone.

Key to Symbols:
↑ = increase
↓ = decrease
↔ = no change

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CCB = calcium channel blockers; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAAs = direct-acting antivirals; DHA = dihydroartemisinin; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; HMG-CoA = hydroxy-methylglutaryl-coenzyme A; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PCP = *Pneumocystis jiroveci* pneumonia; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir

Table 18c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 17, 2017; last reviewed October 17, 2017)
(page 1 of 3)

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.

Note: Interactions associated with didanosine (ddI) and stavudine (d4T) are not included in this table. Please refer to Food and Drug Administration product labels for information regarding interactions between ddI or d4T with other concomitant drugs.

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Cytomegalovirus and Hepatitis B Antivirals			
Adefovir	TDF	No data	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may be increased.
Ganciclovir, Valganciclovir	TDF	No data	Serum concentrations of these drugs and/or TDF may increase. Monitor for dose-related toxicities.
	ZDV	No significant effect	Potential increase in hematologic toxicities.
Hepatitis C Antiviral Agents			
Ledipasvir/sofosbuvir,	TAF	No significant effect	No dose adjustment.
sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/ voxilaprevir	TDF	Ledipasvir ↑ TDF AUC 40%–98% when TDF is given with RPV and EFV. Further ↑ TDF possible if TDF is given with PIs.	No dose adjustment necessary. General recommendations: The safety of increased TDF exposure when ledipasvir/sofosbuvir is coadministered with TDF and a PI/r, ATV/c, or DRV/c has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. Consider using TAF in patients at risk of TDF-associated adverse events. If coadministration with TDF is necessary, monitor for TDF toxicity. **Coadministration of ledipasvir/sofosbuvir with EVG/c/TDF/FTC is not recommended.**
Glecaprevir/Pibrentasvir	TAF, TDF	No significant effect	No dose adjustment.
Ribavirin	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.
INSTIs			
DTG	TAF	TAF AUC ↔	No dose adjustment.
	TDF	TDF AUC ↔ DTG AUC ↔	No dose adjustment.
RAL	TDF	RAL AUC ↑ 49%	No dose adjustment.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, TDF, TAF, ZDV	No significant effect	No dose adjustment.

Table 18c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 17, 2017; last reviewed October 17, 2017)
(page 2 of 3)

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence, continued			
Methadone	ABC	Methadone clearance ↑ 22%	No dose adjustment.
	ZDV	ZDV AUC ↑ 29%–43%	Monitor for ZDV-related adverse effects.
Other			
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.
Anticonvulsants Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	TAF	With carbamazepine: • TAF AUC ↓ 55% ↓ TAF possible with other anticonvulsants	Consider alternative anticonvulsant.
Antimycobacterial Rifabutin, rifampin, rifapentine	TAF	↓ TAF possible	**Coadministration is not recommended.**
Herbal Products St. John's wort	TAF	↓ TAF possible	**Coadministration is not recommended.**
PIs (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 (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) TDF AUC ↑ 24%–37%	**Avoid concomitant use without RTV or COBI.** Dose: • ATV 300 mg daily + (RTV 100 mg or COBI 150 mg) daily when coadministered with TDF 300 mg daily. • If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg daily + (RTV 100 mg or COBI 150 mg) daily. Monitor for TDF-associated toxicity.
	ZDV	With ATV (Unboosted): • ZDV C_{min} ↓ 30% and AUC ↔	Clinical significance unknown.
DRV/c	TAF	TAF 25 mg with DRV/c: • TAF ↔	No dose adjustment.
	TDF	↑ TDF possible	Monitor for TDF-associated toxicity.
DRV/r	TAF	TAF 10 mg with DRV/r: • TAF ↔	No dose adjustment.
	TDF	TDF AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.

Table 18c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 17, 2017; last reviewed October 17, 2017)
(page 3 of 3)

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
PIs (HIV), continued			
LPV/r	TAF	TAF 10 mg with DRV/r: • TAF AUC ↑ 47%	No dose adjustment.
	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC AUC ↓ 35%–44%	Appropriate doses for this combination have not been established.
	TAF	↓ TAF expected	**Coadministration is not recommended.**
	TDF	TDF AUC ↔ TPV/r AUC ↓ 9%–18% and C_{min} ↓ 12%–21%	No dose adjustment.
	ZDV	ZDV AUC ↓ 35% TPV/r AUC ↓ 31%–43%	Appropriate doses for this combination have not been established.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATC/c = atazanavir/cobicistat; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI, c = cobicistat; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitors; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV, r = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 11)

This table provides information on known or predicted pharamacokinetic interactions between INSTIs (DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with COBI. 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.

Concomitant Drug Class/Name	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, Ca supplements, multivitamins).	DTG	DTG AUC ↓ 74% if given simultaneously with antacid DTG AUC ↓ 26% if given 2 hours before antacid	Give DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations.
	EVG/c	EVG AUC ↓ 40%–50% if given simultaneously with antacid EVG AUC ↓ 15%–20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/c/TDF/FTC 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 BID) C_{min} ↓ 32% • RAL (1200 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 1200 mg once daily: Do not coadminister** • RAL 400 mg BID: No dose adjustment or separation necessary
H2-Receptor Antagonists	EVG/c	No significant effect	No dose adjustment.
Proton Pump Inhibitors (PPIs)	DTG	No significant effect	No dose adjustment.
	EVG/c	No significant effect	No dose adjustment.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment.
Anticoagulants and Antiplatelets			
Apixaban	EVG/c	↑ apixaban expected	**Coadministration is not recommended.** Consider alternative antiretroviral (e.g., an unboosted INSTI) or warfarin. If coadministration is necessary, reduce apixaban dose by 50% and monitor for apixaban toxicity.
Betrixaban	EVG/c	↑ betrixaban expected	**Coadministration is not recommended.** Consider alternative antiretroviral (e.g., an unboosted INSTI) or warfarin.
Dabigatran	EVG/c	↑ dabigatran expected Dabigatran AUC ↑ 110%–127% with COBI 150 mg alone	**Coadministration is not recommended.** Consider alternative antiretroviral (e.g., another INSTI) or warfarin.
Edoxaban	EVG/c	↑ edoxaban expected	**Coadministration is not recommended.** Consider alternative antiretroviral (e.g., an unboosted INSTI) or warfarin.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Rivaroxaban	EVG/c	↑ rivaroxaban expected	**Coadministration is not recommended.** Consider alternative antiretroviral (e.g., an unboosted INSTI) or warfarin.
Ticagrelor	EVG/c	↑ ticagrelor expected	**Avoid concomitant use.**
Vorapaxar	EVG/c	↑ vorapaxar expected	**Avoid concomitant use.**
Warfarin	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg BID in treatment-naive or treatment-experienced, INSTI-naive patients. Use alternative anticonvulsant for 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	**Coadministration is not recommended.**
Phenobarbital **Phenytoin**	DTG	↓ DTG possible	**Coadministration is not recommended.**
	EVG/c	↓ EVG/c expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Ethosuximide	EVG/c	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Oxcarbazepine	DTG, EVG/c	↓ INSTI possible ↓ cobicistat possible	Consider alternative anticonvulsant.
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Bupropion	EVG/c	↑ or ↓ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Fluvoxamine	EVG/c	↑ or ↓ EVG possible	Consider alternative antidepressant or ARV.
Lurasidone	EVG/c	↑ lurasidone expected	**Contraindicated.**
Pimozide	EVG/c	↑ pimozide expected	**Contraindicated.**
Quetiapine	EVG/c	↑ quetiapine AUC expected	Initiation of Quetiapine in a Patient Receiving EVG/c: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects. Initiation of EVG/c in a Patient Receiving a Stable Dose of Quetiapine: • Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Selective Serotonin Reuptake Inhibitors (SSRIs) Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	EVG/c	↔ EVG ↔ sertraline	No dose adjustment necessary.
		↑ other SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	RAL	↔ RAL ↔ citalopram ↔ SSRI expected	No dose adjustment necessary.
	DTG	↔ DTG ↔ citalopram ↔ SSRI expected	No dose adjustment necessary.
Tricyclic Antidepressants (TCAs) Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels.
Trazodone	EVG/c	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Antifungals			
Isavuconazole	EVG/c	↑ isavuconazole expected ↑ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.
Itraconazole	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
Posaconazole	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly.
Antihyperglycemics			
Saxagliptin	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/ Saxagliptin	EVG/c	↑ saxagliptin expected	Do not coadminister, as this coformulated drug contains 5 mg of saxagliptin.
Antimycobacterials			
Clarithromycin	EVG/c	↑ clarithromycin possible ↑ COBI possible	CrCl 50–60 mL/min: • Reduce clarithromycin dose by 50% CrCl <50 mL/min: • EVG/c is not recommended

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 4 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin	DTG	Rifabutin (300 mg Once Daily): • DTG AUC ↔ and C_{min} ↓ 30%	No dose adjustment necessary.
	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%, C_{min} ↓ 67%	**Do not coadminister.**
	RAL	RAL AUC ↑ 19%, C_{min} ↓ 20%	No dose adjustment necessary.
Rifampin	DTG	Rifampin with DTG 50 mg BID Compared to DTG 50 mg BID Alone: • DTG AUC ↓ 54%, C_{min} ↓ 72% Rifampin with DTG 50 mg BID Compared to DTG 50 mg Once Daily Alone: • DTG AUC ↑ 33%, C_{min} ↑ 22%	Dose: • DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation. **Alternative to rifampin should be used in patients with certain suspected or documented INSTI-associated resistance substitutions. Consider using rifabutin.**
	EVG/c	Significant ↓ EVG and COBI expected	Contraindicated.
	RAL	RAL 400 mg: • RAL AUC ↓ 40%, C_{min} ↓ 61% Rifampin with RAL 800 mg BID Compared to RAL 400 mg BID Alone: • RAL AUC ↑ 27%, C_{min} ↓ 53%	Dose: • RAL 800 mg BID, instead of 400 mg BID **Do not coadminister RAL 1200 mg once daily with rifampin.** Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	DTG	Significant ↓ DTG expected	**Do not coadminister.**
	EVG/c	Significant ↓ EVG and COBI expected	**Do not coadminister.**
	RAL	Rifapentine 900 mg Once Weekly: • RAL AUC ↑ 71%, C_{min} ↓ 12% Rifapentine 600 mg Once Daily: • RAL C_{min} ↓ 41%	For once-weekly rifapentine, use standard RAL 400 mg BID doses. **Do not coadminister with once-daily rifapentine.**
Cardiac Medications			
Antiarrhythmics Amiodarone, bepridil, digoxin, disopyramide, dronedarone, flecainide, systemic lidocaine, mexilitine, propafenone, quinidine	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and no significant change in AUC	Use antiarrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for antiarrhythmics.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 5 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Bosentan	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.
Beta-blockers (e.g., metoprolol, timolol)	EVG/c	↑ beta-blockers possible	Beta-blocker dose may need to be decreased; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
Calcium Channel Blockers (CCBs)	EVG/c	↑ CCBs possible	Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 18a for diltiazem + ATV/r recommendations.
Dofetilide	DTG	↑ dofetilide expected	**Contraindicated.**
Eplerenone	EVG/c	↑ eplerenone expected	**Contraindicated.**
Ranolazine	EVG/c	↑ ranolazine expected	**Contraindicated.**
Ivabradine	EVG/c	↑ ivabradine expected	**Contraindicated.**
Corticosteroids			
Beclomethasone Inhaled or intranasal	EVG/c	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	EVG/c	↑ glucocorticoid possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Consider an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	EVG/c	↑ glucocorticoids possible ↓ PI possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.**
Dexamethasone Systemic	EVG/c	↓ EVG and COBI possible	Consider an alternative corticosteroid for long-term use or alternative ART. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministered, monitor for adrenal insufficiency and Cushing's syndrome.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 6 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	EVG/c	↑ glucocorticoids expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct Acting Antivirals			
Daclatasvir	DTG	↔ daclatasvir	No dose adjustment necessary.
	EVG/c	↑ daclatasvir	Decrease daclastavir dose to 30 mg once daily.
	RAL	No data	No dose adjustment necessary.
Dasabuvir + Ombitasvir/ Paritaprevir/r	DTG	No data	No dosing recommendations at this time.
	EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dose adjustment necessary.
Elbasvir/Grazoprevir	DTG	↔ elbasvir ↔ grazoprevir ↔ DTG	No dose adjustment necessary.
	EVG/c	↑ elbasvir, grazoprevir expected	**Coadministration is not recommended.**
	RAL	↔ elbasvir ↔ grazoprevir RAL ↔ with elbasvir RAL AUC ↑ 43% with grazoprevir	No dose adjustment necessary.
Glecaprevir/ Pibrentasvir	DTG, RAL	No significant effect	No dose adjustment necessary.
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment necessary.
Ledipasvir/Sofosbuvir	EVG/c/ TDF/ FTC	↑ TDF and ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/ TAF/ FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment necessary.
	DTG, RAL	↔ DTG or RAL	No dose adjustment necessary.
Simeprevir	DTG	↔ expected	No dose adjustment necessary.
	EVG/c	↑ simeprevir expected	**Coadministration is not recommended.**
	RAL	↔ expected	No dose adjustment necessary.
Sofosbuvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/Velpatasvir	All INSTIs	↔ expected	No dose adjustment necessary.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 7 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct Acting Antivirals, continued			
Sofosbuvir/ Velpatasvir/ Voxilaprevir	EVG/c	When Given with Sofosbuvir/Velpatasvir/ Voxilaprevir (400/100/100 mg) + Voxilaprevir 100 mg: • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	DTG	↓ DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI possible	**Contraindicated.**
Hormonal Therapies			
Hormonal Contraceptives	DTG, RAL	↔ ethinyl estradiol, norgestimate, and DTG or RAL	No dose adjustment necessary.
	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 can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method.
		↑ drospirenone possible	Clinical monitoring is recommended, due to the potential for hyperkalemia.
Menopausal Hormone Replacement Therapy	DTG, RAL	With estradiol or conjugated estrogen (equine and synthetic): ↓ estrogen possible ↔ drospirenone, medroxyprogesterone, or micronized progesterone expected	No dose adjustment necessary.
	EVG/c	↓ estrogen possible ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Gender-Affirming Hormone Therapy	DTG, RAL	↔ estrogen expected	No dose adjustment necessary.
	DTG, EVG/c, RAL	↔ finasteride, goserelin, leuprolide acetate, spironolactone expected	
	EVG/c	↓ estradiol possible ↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	EVG/c	↑ testosterone possible	Monitor masculinizing effects of testosterone and for adverse effects and adjust testosterone dose as necessary.
	DTG, RAL	↔ testosterone expected	No dose adjustment necessary.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 8 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors			
Atorvastatin	EVG/c	↑ atorvastatin AUC 2.6-fold and C_{max} 2.3-fold	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
Lovastatin	EVG/c	Significant ↑ lovastatin expected	**Contraindicated**.
Pitavastatin, Pravastatin	EVG/c	No data	No dosage recommendation
Rosuvastatin	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities.
Simvastatin	EVG/c	Significant ↑ simvastatin expected	**Contraindicated**.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	EVG/c	↑ immunosuppressant possible	Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	EVG/c	Buprenorphine AUC ↑ 35%, C_{max} ↑ 12%, and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42%, C_{max} ↑ 24%, and C_{min} ↑ 57%	No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ observed (sublingual) ↔ expected (implant)	No dose adjustment necessary.
Methadone	DTG	No significant effect	No dose adjustment necessary.
	EVG/c	No significant effect	No dose adjustment necessary.
	RAL	No significant effect	No dose adjustment necessary.
Neuroleptics			
Perphenazine, Risperidone, Thioridazine	EVG/c	↑ neuroleptic possible	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary.
PDE5 Inhibitors			
Avanafil	EVG/c	No data	Coadministration is not recommended.
Sildenafil	EVG/c	↑ sildenafil expected	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of PAH: • **Contraindicated.**

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 9 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Tadalafil	EVG/c	↑ tadalafil expected	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 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 and increase to 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 40 mg once daily based on tolerability.
Vardenafil	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	EVG/c	↑ benzodiazepines possible	Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor. Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam.
Midazolam, Triazolam	DTG	With DTG 25 mg: • midazolam AUC ↔	No dose adjustment necessary.
	EVG/c	↑ midazolam expected ↑ triazolam expected	**Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c.** Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered.
Suvorexant	EVG/c	↑ suvorexant expected	**Coadministration is not recommended.**
Zolpidem	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction may be necessary.
Miscellaneous Drugs			
Alfuzosin	EVG/c	↑ alfuzosin expected	**Contraindicated.**
Calcifediol	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations should be closely monitored.
Cisapride	EVG/c	↑ cisapride expected	**Contraindicated.**

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 10 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
Colchicine	EVG/c	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** For Treatment of Gout Flares: • Colchicine 0.6 mg for 1 dose, followed by 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 BID, decrease to colchicine 0.3 mg once daily. If regimen 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 BID.
Ergot Derivatives	EVG/c	↑ dihydroergotamine, ergotamine, methylergonovine expected	**Contraindicated.**
Dronabinol	EVG/c	↑dronabinol possible	Monitor for dronabinol-related adverse effects.
Eluxadoline	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse effects.
Flibanserin	EVG/c	↑ flibanserin expected	**Contraindicated.**
Metformin	DTG	DTG 50 mg Once Daily + Metformin 500 mg BID: • Metformin AUC ↑ 79%, C_{max} ↑ 66% DTG 50 mg BID + Metformin 500 mg BID: • Metformin AUC↑ 2.4-fold, C_{max} ↑ 2-fold	Start metformin at lowest dose and titrate based on glycemic control. Monitor for metformin adverse effects. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse effects of metformin.
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.	All INSTIs	↓ INSTI possible DTG ↔ when administered with Ca or Fe supplement simultaneously with food	If coadministration is necessary, give INSTI at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy. DTG and supplements containing Ca or Fe can be taken simultaneously with food. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
Salmeterol	EVG/c	↑ salmeterol possible	**Do not coadminister**, due to potential increased risk of salmeterol-associated cardiovascular events.

Table 18d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 17, 2017; last reviewed October 17, 2017) (page 11 of 11)

Key to Acronyms: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; AUC = area under the curve; BID = twice daily; Ca = calcium; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI, c = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; Fe = iron; FTC = emtricitabine; GI = gastrointestinal; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PPI = proton pump inhibitor; PTH = parathyroid hormone; r = ritonavir; RAL = raltegravir; TDF = tenofovir disoproxil fumarate; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; Zn = zinc

Table 18e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 3)

In the table below, "no dosage adjustment" indicates that the Food and Drug Administration-approved dose of MVC 300 mg twice daily should be used. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV 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.

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungals			
Isavuconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID.
Itraconazole	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Posaconazole	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID.
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, no dosage adjustment. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Dose: • MVC 600 mg BID If used with a strong CYP3A inhibitor, use MVC 300 mg BID.
Rifapentine	MVC	↓ MVC expected	**Do not coadminister.**
Hepatitis C Direct-Acting Antivirals			
Daclatasvir	MVC	↔ MVC expected ↔ Daclatasvir expected	No dosage adjustment.
Dasabuvir + Ombitasvir/ Paritaprevir/RTV	MVC	↑ MVC expected	**Do not coadminister.**
Elbasvir/Grazoprevir	MVC	No data	No dosing recommendations at this time.
Ledipasvir/Sofosbuvir	MVC	↔ MVC expected	No dosage adjustment.
Glecaprevir/Pibrentasvir	MVC	↔ MVC expected	No dosage adjustment.
Simeprevir	MVC	↔ MVC expected	No dosage adjustment.
Sofosbuvir	MVC	↔ MVC expected	No dosage adjustment.
Sofosbuvir/Velpatasvir	MVC	↔ MVC expected	No dosage adjustment.

Table 18e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 3)

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antivirals, continued			
Sofosbuvir/Velpatasvir/ Voxilaprevir	MVC	↔ MVC expected	No dosage adjustment.
Herbal Products			
St. John's Wort	MVC	↓ MVC expected	**Do not coadminister.**
Hormonal Therapies			
Hormonal Contraceptives	MVC	↔ Ethinyl estradiol or levonorgestrel	No dosage adjustment.
Menopausal Hormone Replacement Therapy	MVC	↔ MVC or hormone replacement therapies expected	No dosage adjustment.
Gender-Affirming Hormone Therapies	MVC	↔ MVC or gender-affirming hormones expected	No dosage adjustment.
ARV Drugs			
INSTIs			
EVG/c	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
RAL	MVC	MVC AUC ↓ 21% RAL AUC ↓ 37%	No dosage adjustment.
NNRTIs			
EFV	MVC	MVC AUC ↓ 45%	Dose: • MVC 600 mg BID
ETR	MVC	MVC AUC ↓ 53%	Dose: • MVC 600 mg BID in the absence of a potent CYP3A inhibitor
NVP	MVC	MVC AUC ↔	Without HIV PI: • MVC 300 mg BID With HIV PI (except TPV/r): • MVC 150 mg BID
PIs			
ATV +/- RTV or COBI	MVC	With Unboosted ATV: • MVC AUC ↑ 257% With (ATV 300 mg + RTV 100 mg) Once Daily: • MVC AUC ↑ 388%	Dose: • MVC 150 mg BID

Table 18e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 3)

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PIs, continued			
DRV/c or DRV/r	MVC	With (DRV 600 mg + RTV 100 mg) BID: • MVC AUC ↑ 305% With (DRV 600 mg + RTV 100 mg) BID and ETR: • MVC AUC ↑ 210%	Dose: • MVC 150 mg BID
LPV/r	MVC	MVC AUC ↑ 295% With LPV/r and EFV: • MVC AUC ↑ 153%	Dose: • MVC 150 mg BID
RTV	MVC	With RTV 100 mg BID: • MVC AUC ↑ 161%	Dose: • MVC 150 mg BID
TPV/r	MVC	With (TPV 500 mg + RTV 200 mg) BID: • MVC AUC ↔	No dosage adjustment.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; AUC = area under the curve; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Table 19a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors[a] (Last updated October 17, 2017; last reviewed October 17, 2017) (Page 1 of 2)

Note: Delavirdine (DLV), fosamprenavir (FPV), indinavir (IDV), nelfinavir (NFV), and saquinavir (SQV) are **not** included in this table. Please refer to the Food and Drug Administration product labels for DLV, FPV, IDV, NFV, and SQV for information regarding drug interactions.

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
ATV Unboosted	**PK Data**	EFV: No significant change ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ATV AUC ↓ 17% and C_{min} ↓ 47%	↓ ATV possible	↑ RPV possible
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/c	**PK Data**	↓ ATV possible ↓ COBI possible	↓ ATV possible ↓ COBI possible	↓ ATV possible ↓ COBI possible	↑ RPV possible ↔ ATV expected
	Dose	EFV standard dose In ART-Naive Patients: • ATV 400 mg + COBI 150 mg once daily • **Do not use coformulated ATV/c 300 mg/150 mg.** In ART-Experienced Patients: • **Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/r	**PK Data**	(ATV 400 mg + RTV 100 mg) Once Daily: • ATV concentrations similar to (ATV 300 mg + RTV 100 mg) without EFV	(ATV 300 mg + RTV 100 mg) Once Daily: • ETR AUC and C_{min} both ↑ ~30% • ATV AUC ↔ and C_{min} ↓ 18%	(ATV 300 mg + RTV 100 mg) Once Daily: • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV possible
	Dose	EFV standard dose In ART-Naive Patients: • (ATV 400 mg + RTV 100 mg) once daily In ART-Experienced Patients: • **Do not coadminister.**	ETR standard dose (ATV 300 mg + RTV 100 mg) once daily	**Do not coadminister.**	Standard doses
DRV/c	**PK Data**	↓ DRV possible ↓ COBI possible	↓ DRV possible ↓ COBI possible	↓ DRV possible ↓ COBI possible	↔ DRV expected ↑ RPV possible
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses

Table 19a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors[a] (Last updated October 17, 2017; last reviewed October 17, 2017) (Page 2 of 2)

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
DRV/r	**PK Data**	With (DRV 300 mg + RTV 100 mg) BID: • EFV AUC ↑ 21% • DRV AUC ↓ 13% and C_{min} ↓ 31%	ETR 100 mg BID with (DRV 600 mg + RTV 100 mg) BID: • ETR AUC ↓ 37% and C_{min} ↓ 49% • DRV: No significant change	With (DRV 400 mg + RTV 100 mg) BID: • NVP AUC ↑ 27% and C_{min} ↑ 47% • DRV AUC ↑ 24%[b]	RPV 150 mg Once Daily with (DRV 800 mg + RTV 100 mg) Once Daily: • RPV AUC ↑ 130% and C_{min} ↑ 178% • DRV: No significant change
	Dose	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard doses Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	Standard doses	Standard doses
LPV/r	**PK Data**	With LPV/r Tablets 500/125 mg[c] BID: • LPV concentration similar to that with LPV/r 400/100 mg BID without EFV	With LPV/r Tablets: • ETR AUC ↓ 35% (comparable to the decrease with DRV/r) • LPV AUC ↓ 13%	With LPV/r Capsules: • LPV AUC ↓ 27% and C_{min} ↓51%	RPV 150 mg Once Daily with LPV/r Capsules: • RPV AUC ↑ 52% and C_{min} ↑ 74% • LPV: No significant change
	Dose	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID EFV standard dose	Standard doses	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID NVP standard dose	Standard doses
TPV Always use with RTV	**PK Data**	With (TPV 500 mg + RTV 100 mg) BID: • EFV ↔ • TPV AUC ↓ 31% and C_{min} ↓ 42% With (TPV 750 mg + RTV 200 mg) BID: • EFV and TPV: ↔	With (TPV 500 mg + RTV 200 mg) BID: • ETR AUC ↓ 76% and C_{min} ↓ 82% • TPV AUC ↑ 18% and C_{min} ↑ 24%	With (TPV 250 mg + RTV 200 mg) BID or with (TPV 750 mg + RTV 100 mg) BID: • NVP: ↔ • TPV: ↔ expected	↑ RPV possible
	Dose	Standard doses	**Do not coadminister.**	Standard doses	Standard doses

[a] Approved dose for RPV is 25 mg once daily. Most PK studies were performed using 75 mg to 150 mg RPV per dose.

[b] Based on between-study comparison.

[c] Use a combination of two LPV/r 200/50 mg tablets plus one LPV/r 100/25 mg tablet to make a total dose of LPV/r 500/125 mg.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{min} = minimum plasma concentration; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir

Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 3)

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV 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.

ARV Drugs by Drug Class		INSTIs		
		DTG	EVG/c	RAL
NNRTIs				
EFV	**PK Data**	With DTG 50 mg Once Daily: • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, EFV possible	With RAL 400 mg BID: • RAL AUC ↓ 36% and C_{min} ↓ 21% With RAL 1200 mg Once Daily: • RAL AUC ↓ 14% and C_{min} ↔
	Dose	In Patients Without INSTI Resistance: • DTG 50 mg BID In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance: **• Consider alternative combination.**	**Do not coadminister.**	Standard doses
ETR	**PK Data**	ETR 200 mg BID + DTG 50 mg Once Daily: • DTG AUC ↓ 71% and C_{min} ↓ 88% ETR 200 mg BID with (DRV 600 mg + RTV 100 mg) BID and DTG 50 mg Once Daily: • DTG AUC ↓ 25% and C_{min} ↓ 37% ETR 200 mg BID with (LPV 400 mg + RTV 100 mg) BID and DTG 50 mg Once Daily: • DTG AUC ↑ 11% and C_{min} ↑ 28%	↑ or ↓ EVG, COBI, ETR possible	ETR 200 mg BID + RAL 400 mg BID: • ETR C_{min} ↑ 17% • RAL C_{min} ↓ 34%
	Dose	**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 BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not coadminister.**	RAL 400 mg BID **Coadministration with RAL 1200 mg once daily is not recommended.**
NVP	**PK Data**	With DTG 50 mg Once Daily: • DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, NVP possible	No data
	Dose	Standard doses	**Do not coadminister.**	Standard doses

Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 3)

ARV Drugs by Drug Class		INSTIs		
		DTG	EVG/c	RAL
NNRTIs, continued				
RPV	**PK Data**	With DTG 50 mg Once Daily: • DTG AUC ↔ and C_{min} ↑ 22% • RPV AUC ↔ and C_{min} ↑ 21%	↑ or ↓ EVG, COBI, RPV possible	• RPV ↔ • RAL C_{min} ↑ 27%
	Dose	Standard doses	**Do not coadminister.**	Standard doses
PIs				
ATV/c	**PK Data**	No data	ATV/c + EVG/c: • No data	No data
	Dose	Standard doses	**Do not coadminister.**	Standard doses
ATV +/- RTV	**PK Data**	Unboosted ATV + DTG 30 mg Once Daily: • DTG AUC ↑ 91% and C_{min} ↑ 180% (ATV 300 mg + RTV 100 mg) Once Daily + DTG 30 mg Once Daily: • DTG AUC ↑ 62% and C_{min} ↑ 121%	↑ or ↓ EVG, COBI, ATV possible	With Unboosted ATV: • RAL AUC ↑ 72% With Unboosted ATV and RAL 1200 mg • RAL AUC ↑ 67% With (ATV 300 mg + RTV 100 mg) Once Daily: • RAL AUC ↑ 41%
	Dose	Standard doses	**Do not coadminister.**	Standard doses
DRV/c	**PK Data**	DTG 50 mg Once Daily and DRV/r Once Daily Switched to DRV/c: • DTG C_{min} ↑ 100%	DRV/c + EVG/c: • ↓ EVG possible	No data
	Dose	Standard doses	**Do not coadminister.**	Standard doses
DRV/r	**PK Data**	(DRV 600 mg + RTV 100 mg) BID with DTG 30 mg Once Daily: • DTG AUC ↓ 22% and C_{min} ↓ 38%	↑ or ↓ EVG, COBI, DRV possible	With (DRV 600 mg + RTV 100 mg) BID: • RAL AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Standard doses	**Do not coadminister.**	Standard doses
LPV/r	**PK Data**	With (LPV 400 mg + RTV 100 mg) BID and DTG 30 mg Once Daily: • DTG: No significant effect	↑ or ↓ EVG, COBI, LPV possible RTV and COBI have similar effects on CYP3A.	↓ RAL ↔ LPV/r
	Dose	Standard doses	**Do not coadminister.**	Standard doses
TPV/r	**PK Data**	With (TPV 500 mg + RTV 200 mg) BID and DTG 50 mg Once Daily: • DTG AUC ↓ 59% and C_{min} ↓ 76%	↑ or ↓ EVG, COBI, TPV possible RTV and COBI have similar effects on CYP3A.	With (TPV 500 mg + RTV 200 mg) BID and RAL 400 mg BID: • RAL AUC ↓ 24% and C_{min} ↓ 55%
	Dose	In Patients Without INSTI Resistance: • DTG 50 mg BID In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance: • **Consider alternative combination.**	**Do not coadminister.**	RAL 400 mg BID **Coadministration with RAL 1200 mg once daily is not recommended.**

Table 19b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 3)

[a] Refer to DTG product labeling for details.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{min} = minimum plasma concentration; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Conclusion (Last updated January 28, 2016; last reviewed January 28, 2016)

The Panel has carefully reviewed results from clinical HIV therapy trials and considered how they affect appropriate care guidelines. HIV care is complex and rapidly evolving. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. Absent such evidence, the Panel has attempted to base recommendations on reasonable options for HIV care.

HIV care requires partnerships and open communication. Guidelines are only a starting point for medical decision making involving informed providers and patients. Although guidelines can identify some parameters of high-quality care, they cannot substitute for sound clinical judgment.

As further research is conducted and reported, these guidelines will be modified. The Panel anticipates continued progress in refining antiretroviral therapy regimens and strategies. The Panel hopes these guidelines are useful and is committed to their continued revision and improvement.

Appendix A: Key to Acronyms (Last updated October 17, 2017; last reviewed October 17, 2017)

Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IDV	indinavir
LPV	lopinavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	zidovudine

General Terms

Abbreviation	Definition
17-BMP	beclomethasone 17-monopropionate
ADAP	AIDS drug assistance program
Ag/Ab	antigen/antibody
Al	aluminum
ALT	alanine aminotransferase

ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
AWP	average wholesale price
BID	twice daily
BMD	bone mineral density
BUN	blood urea nitrogen
Ca	calcium
$CaCO_3$	calcium carbonate
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CCB	calcium channel blockers
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAA	direct-acting antiviral
DHA	dihydroartemisinin
DILI	drug-induced liver injury
DMPA	depot medroxyprogesterone acetate
DOT	directly observed therapy
EBV	Epstein-Barr virus
EC	enteric coated
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
Fe	iron

FI	fusion inhibitor
GAZT	azidothymidine glucuronide
GI	gastrointestinal
HAD	HIV-associated dementia
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCO_3	bicarbonate
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV RNA	HIV viral load
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVAN	HIV-associated nephropathy
HLA	human leukocyte antigen
HMG-CoA	hydroxy-methylglutaryl-coenzyme A
HRT	hormone replacement therapy
HSR	hypersensitivity reaction
HTLV-1	human T-lymphotropic virus-1
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
K	potassium
KS	Kaposi's sarcoma
LDL	low-density lipoprotein
LLOD	lower limits of detection
MAC	*Mycobacterium avium* complex
MATE	multidrug and toxin extrusion transporter
Mg	magnesium
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
msec	millisecond
MTR	multi-tablet regimen
Na	sodium

NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OATP	organic anion-transporting polypeptide
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
OI	opportunistic infection
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
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
q(n)d	every (n) days
q(n)h	every (n) hours
QTc	QT corrected for heart rate
RNA	ribonucleic acid
RT	reverse transcriptase
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
STR	single-tablet regimen
TB	tuberculosis
TCA	tricyclic antidepressant
TdP	torsades de pointes
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times a day
UGT	uridine diphosphate glucuronosyltransferase
VPA	valproic acid
WHO	World Health Organization
XR	extended release
Zn	zinc

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic available. **Also available as a component of fixed-dose combinations (by trade name and abbreviation)**:	Ziagen: • 300 mg tablet • 20 mg/mL oral solution	Ziagen: • 600 mg once daily *or* • 300 mg BID Take without regard to meals.	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 7).	1.5 hours/12–26 hours	• HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC. • For patients with history of HSR, rechallenge **is not recommended**. • Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir (ABC/ZDV/3TC) **Note:** Generic available.	Trizivir: • (ABC 300 mg + ZDV 300 mg + 3TC 150 mg) tablet	Trizivir: • 1 tablet BID			
Epzicom (ABC/3TC) **Note:** Generic available.	Epzicom: • (ABC 600 mg + 3TC 300 mg) tablet	Epzicom: • 1 tablet once daily			
Triumeq (ABC/3TC/DTG)	Triumeq: • (ABC 600 mg + 3TC 300 mg + DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
Didanosine (ddI) *Videx* *Videx EC* **Note:** Generic available; dose same as Videx or Videx EC.	Videx EC: • 125, 200, 250, and 400 mg capsules Videx: • 10 mg/mL oral solution	Body Weight ≥60 kg: • 400 mg once daily *With TDF:* • 250 mg once daily Body Weight <60 kg: • 250 mg once daily *With TDF:* • 200 mg once daily Take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is BID (total daily dose divided into 2 doses).	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.5 hours/ >20 hours	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis with or without pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with noncirrhotic portal hypertension; in some cases, patients presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Emtriva: • 200 mg hard gelatin capsule • 10 mg/mL oral solution	Emtriva *Capsule:* • 200 mg once daily *Oral Solution:* • 240 mg (24 mL) once daily Take without regard to meals.	Renal excretion: 86% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	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.
Atripla (FTC/EFV/TDF)	Atripla: • (FTC 200 mg + EFV 600 mg + TDF 300 mg) tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera (FTC/RPV/TDF)	Complera: • (FTC 200 mg + RPV 25 mg + TDF 300 mg) tablet	Complera: • 1 tablet once daily with a meal			
Descovy (FTC/TAF)	Descovy: • (FTC 200 mg + TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
Genvoya (FTC/EVG/c/TAF)	Genvoya: • (FTC 200 mg + EVG 150 mg + COBI 150 mg + TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food			
Odefsey (FTC/RPV/TAF)	Odefsey: • (FTC 200 mg + RPV 25 mg + TAF 25 mg) tablet	Odefsey: • 1 tablet once daily with a meal			
Stribild (FTC/EVG/c/TDF)	Stribild: • (FTC 200 mg + EVG 150 mg + COBI 150 mg + TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food			
Truvada (FTC/TDF)	Truvada: • (FTC 200 mg + TDF 300 mg) tablet	Truvada: • 1 tablet once daily			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Lamivudine (3TC) *Epivir* **Note:** Generic available. **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Epivir: • 150 and 300 mg tablets • 10 mg/mL oral solution	Epivir: • 300 mg once daily *or* • 150 mg BID Take without regard to meals.	Renal excretion: 70% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	5–7 hours/ 18–22 hours	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue 3TC.
Combivir (3TC/ZDV) **Note:** Generic available.	Combivir: • (3TC 150 mg + ZDV 300 mg) tablet	Combivir: • 1 tablet BID			
Epzicom (3TC/ABC) **Note:** Generic available.	Epzicom: • (3TC 300 mg + ABC 600 mg) tablet	Epzicom: • 1 tablet once daily			
Trizivir (3TC/ZDV/ABC) **Note:** Generic available.	Trizivir: • (3TC 150 mg + ZDV 300 mg + ABC 300 mg) tablet	Trizivir: • 1 tablet BID			
Triumeq (3TC/ABC/DTG)	Triumeq: • (3TC 300 mg + ABC 600 mg + DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
Stavudine (d4T) *Zerit* **Note:** Generic available.	Zerit: • 15, 20, 30, and 40 mg capsules • 1 mg/mL oral solution	Body Weight ≥60 kg: • 40 mg BID Body Weight <60 kg: • 30 mg BID Take without regard to meals. **Note:** WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1 hour/ 7.5 hours	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Alafenamide (TAF) *Vemlidy* **Note:** Available as a 25-mg tablet for the treatment of HBV. **Fixed-dose combinations for HIV are listed below (by trade name and abbreviation):**	See fixed-dose combinations for HIV treatment below.	See fixed-dose combinations for HIV treatment below.	Metabolized by cathepsin A; P-glycoprotein substrate Not recommended in patients with CrCl <30 mL/min.	0.5 hours/ 150–180 hours	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy (less likely than from TDF) • Osteomalacia, decrease in bone mineral density (lesser effect than from TDF) • Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue TAF. • Diarrhea, nausea, headache
Descovy (TAF/FTC)	Descovy: • (FTC 200 mg + TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
Genvoya (TAF/EVG/c/FTC)	Genvoya: • (TAF 10 mg + EVG 150 mg + COBI 150mg + FTC 200 mg) tablet	Genvoya: • 1 tablet once daily with food			
Odefsey (TAF/RPV/FTC)	Odefsey: • (TAF 25 mg + RPV 25 mg + FTC 200 mg) tablet	Odefsey: • 1 tablet once daily with a meal			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Disoproxil Fumarate (TDF) Viread **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Viread: • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder	Viread: • 300 mg once daily, *or* • 7.5 level scoops once daily (dosing scoop dispensed with each prescription; 1 level scoop contains 1 g of oral powder) • Take without regard to meals. 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.**	Renal excretion is primary route of elimination. Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	17 hours/ >60 hours	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy • Osteomalacia, decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla (TDF/EFV/FTC)	Atripla: • (TDF 300 mg + EFV 600 mg + FTC 200 mg) tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera (TDF/RPV/FTC)	Complera: • (TDF 300 mg + RPV 25 mg + FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			
Stribild (TDF/EVG/c/FTC)	Stribild: • (TDF 300 mg + EVG 150 mg + COBI 150 mg + FTC 200 mg) tablet	Stribild: • 1 tablet once daily • Take with food.			
Truvada (TDF/FTC)	Truvada: • (TDF 300 mg + FTC 200 mg) tablet	Truvada: • 1 tablet once daily • Take without regard to meals.			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 6 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Zidovudine (ZDV) *Retrovir* **Note:** Generic available. **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Retrovir: • 100 mg capsule • 300 mg tablet (only available as generic) • 10 mg/mL intravenous solution • 10 mg/mL oral solution	Retrovir: • 300 mg BID, *or* • 200 mg TID • Take without regard to meals.	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.1 hours/ 7 hours	• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir (ZDV/3TC) **Note:** Generic available.	Combivir: • (ZDV 300 mg + 3TC 150 mg) tablet	Combivir: • 1 tablet BID • Take without regard to meals.			
Trizivir (ZDV/3TC/ABC) **Note:** Generic available.	Trizivir: • (ZDV 300 mg + 3TC 150 mg + ABC 300 mg) tablet	Trizivir: • 1 tablet BID • Take without regard to meals.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; BID = twice daily; COBI, c = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; WHO = World Health Organization; ZDV = zidovudine

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 2)

Note: Delavirdine (DLV) is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Efavirenz (EFV) *Sustiva* **Also available as a component of a fixed-dose combination (by trade name and abbreviation):**	Sustiva: • 50 and 200 mg capsules • 600 mg tablet	Sustiva: • 600 mg once daily, at or before bedtime • Take on an empty stomach to reduce side effects.	Metabolized by CYPs 2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/ inhibitor (more an inducer than an inhibitor) CYP2C9 and 2C19 inhibitor; 2B6 inducer	40–55 hours	• Rash[c] • Neuropsychiatric symptoms[d] • Hepatotoxicity • Hyperlipidemia • False-positive results with some cannabinoid and benzodiazepine screening assays reported. • Teratogenic in nonhuman primates • QT interval prolongation
Atripla (EFV/TDF/FTC)	Atripla: • (EFV 600 mg + TDF 300 mg + FTC 200 mg) tablet	Atripla: • 1 tablet once daily, at or before bedtime			
Etravirine (ETR) *Intelence*	• 25, 100, and 200 mg tablets	• 200 mg BID • Take following a meal.	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 hours	• Rash, including Stevens-Johnson syndrome[c] • HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported. • Nausea

Nevirapine (NVP) *Viramune*
Viramune XR
 	
Note: Generic available
	• 200 mg tablet
	• 400 mg XR tablet
	• 50 mg/5 mL oral suspension
		• 200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID, or 400 mg (Viramune XR tablet) once daily
		• Take without regard to meals.
		• 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 period until rash resolves but not longer than 28 days total.
			CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% excreted in feces	25–30 hours	• Rash, including Stevens-Johnson syndrome[c]
					• Symptomatic hepatitis, including fatal hepatic necrosis, has been reported:
					  • Rash reported in approximately 50% of cases.
					  • 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.

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 2)

Note: Delavirdine (DLV) is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Rilpivirine (RPV) *Edurant* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Edurant: • 25 mg tablet	Edurant: • 25 mg once daily • Take with a meal.	CYP3A4 substrate	50 hours	• Rash[c] • Depression, insomnia, headache • Hepatotoxicity • QT interval prolongation
Complera (RPV/TDF/FTC)	Complera: • (RPV 25 mg + TDF 300 mg + FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			
Odefsey (RPV/TAF/FTC)	Odefsey: • (RPV 25 mg + TAF 25 mg + FTC 200 mg) tablet	Odefsey: • 1 tablet once daily • Take with a meal.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

[c] Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.

[d] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

Key to Acronyms: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Atazanavir (ATV) *Reyataz* **Also available as a component of a fixed-dose combination (by trade name and abbreviation):**	Reyataz: • 100, 150, 200, and 300 mg capsules • 50 mg single packet oral powder	In ARV-Naive Patients: • (ATV 300 mg + RTV 100 mg) once daily; *or* • ATV 400 mg once daily With TDF or in ARV-Experienced Patients: • (ATV 300 mg + RTV 100 mg) once daily With EFV in ARV-Naive Patients: • (ATV 400 mg + RTV 100 mg) once daily Take with food. For recommendations on dosing with H2 antagonists and PPIs, refer to Table 18a.	CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7 hours	Room temperature (up to 25º C or 77º F)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients with underlying conduction defects or in patients on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting) • Skin rash • Increase in serum creatinine (with COBI)
Evotaz (ATV/c)	Evotaz: • (ATV 300 mg + COBI 150 mg) tablet	Evotaz: • 1 tablet once daily • Take with food. With TDF: • Not recommended for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	ATV: As above COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor			

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Darunavir (DRV) *Prezista* **Also available as a component of a fixed-dose combination (by trade name and abbreviation):**	• 75, 150, 600, and 800 mg tablets • 100 mg/ mL oral suspension	In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations: • (DRV 800 mg + RTV 100 mg) once daily In ARV-Experienced Patients with 1 or More DRV Resistance Mutations: • (DRV 600 mg + RTV 100 mg) BID Unboosted DRV **is not recommended.** Take with food.	CYP3A4 inhibitor and substrate CYP2C9 inducer	15 hours (when combined with RTV)	Room temperature (up to 25º C or 77º F)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)
Prezcobix (DRV/c)	Prezcobix: • (DRV 800 mg + COBI 150 mg) tablet	Prezcobix: • 1 tablet once daily • Take with food. **Not recommended** for patients with 1 or more DRV resistance-associated mutations. With TDF: • Not recommended for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	DRV: As above COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor			

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Fosamprenavir (FPV) *Lexiva* (a prodrug of APV)	• 700 mg tablet • 50 mg/ mL oral suspension	In ARV-Naive Patients: • FPV 1400 mg BID, *or* • (FPV 1400 mg + RTV 100–200 mg) once daily, *or* • (FPV 700 mg + RTV 100 mg) BID In PI-Experienced Patients (Once-Daily Dosing **Not Recommended**): • (FPV 700 mg + RTV 100 mg) BID With EFV: • (FPV 700 mg + RTV 100 mg) BID, *or* • (FPV 1400 mg + RTV 300 mg) once daily *Tablet:* • Without RTV tablet: Take without regard to meals. • With RTV tablet: Take with meals. *Oral Suspension:* • Take without food.	APV is a CYP3A4 substrate, inhibitor, and inducer. Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7.7 hours (APV)	Room temperature (up to 25º C or 77º F)	• Skin rash (12% to 19%): FPV has a sulfonamide moiety. • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
Indinavir (IDV) *Crixivan*	• 100, 200, and 400 mg capsules	• 800 mg every 8 hours • Take 1 hour before or 2 hours after meals; may take with skim milk or a low-fat meal. With RTV: • (IDV 800 mg + RTV 100–200 mg) BID • Take without regard to meals.	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	1.5–2 hours	Room temperature (15º to 30º C or 59º to 86º F) Protect from moisture.	• Nephrolithiasis • GI intolerance, nausea • Hepatitis • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	Tablets: • (LPV 200 mg + RTV 50 mg), *or* • (LPV 100 mg + RTV 25 mg) Oral Solution: • Each 5 mL contains (LPV 400 mg + RTV 100 mg). • Oral solution contains 42% alcohol.	• (LPV 400 mg + RTV 100 mg) BID, *or* • (LPV 800 mg + RTV 200 mg) once daily Once-daily dosing **is not recommended** for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. With EFV or NVP (PI-Naive or PI Experienced Patients): • LPV/r 500/125 mg tablets BID (use a combination of 2 LPV/r 200/50 mg tablets + 1 LPV/r 100/25 mg tablet to make a total dose of LPV/r 500/125 mg), *or* • LPV/r 533/133 mg oral solution BID *Tablet:* • Take without regard to meals. *Oral Solution:* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	Oral tablet is stable at room temperature. Oral solution is stable at 2° to 8° C (36° to 46° F) until date on label and is stable for up to 2 months when stored at room temperature (up to 25° C or 77° F).	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/ diabetes mellitus • Fat maldistribution • Possible increased 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.
Nelfinavir (NFV) *Viracept*	• 250 and 625 mg tablets • 50 mg/g oral powder	• 1250 mg BID, *or* • 750 mg TID Dissolve tablets in a small amount of water, mix admixture well, and consume immediately. Take with food.	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor	3.5–5 hours	Room temperature (15° to 30° C or 59° to 86° F)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Ritonavir (RTV) *Norvir* **Also available as a component of a fixed-dose combination (see lopinavir/ ritonavir).**	• 100 mg tablet • 100 mg soft gel capsule • 80 mg/mL oral solution • 100 mg single-packet oral powder Oral solution contains 43% alcohol.	As PK Booster (or Enhancer) for Other PIs: • 100–400 mg per day in 1 or 2 divided doses (refer to other PIs for specific dosing recommendations). *Tablet:* • Take with food. *Capsule and Oral Solution:* • To improve tolerability, take with food if possible.	CYP3A4 > 2D6 substrate; potent 3A4, 2D6 inhibitor; inducer of CYPs 1A2, 2C8, 2C9, and 2C19 and UGT1A1	3–5 hours	Tablets and oral powder do not require refrigeration. Refrigerate capsules. Capsules can be left at room temperature (up to 25° C or 77° F) for up to 30 days. **Oral solution should not be refrigerated.**	• GI intolerance, nausea, vomiting, diarrhea • Paresthesia (circumoral and extremities) • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir (SQV) *Invirase*	• 500 mg tablet • 200 mg capsule	• (SQV 1000 mg + RTV 100 mg) BID Unboosted SQV **is not recommended.** Take with meals or within 2 hours after a meal.	CYP3A4 substrate	1–2 hours	Room temperature (15° to 30° C or 59° to 86° F)	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation. Torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV.

Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 6 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Tipranavir (TPV) *Aptivus*	• 250 mg capsule • 100 mg/mL oral solution	• (TPV 500 mg + RTV 200 mg) BID Unboosted TPV **is not recommended.** With RTV Tablets: • Take with meals. With RTV Capsules or Solution: • Take without regard to meals.	CYP P450 3A4 inducer and substrate CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer Net effect when combined with RTV (CYP3A4, 2D6 inhibitor)	6 hours after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25° C or 77° F) for up to 60 days. **Oral solution should not be refrigerated or frozen** and should be used within 60 days after bottle is opened.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported. Monitor patients closely, especially those with underlying liver diseases. • Skin rash (3% to 21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, and the use of anticoagulant or antiplatelet agents (including vitamin E). • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; BID = twice daily; COBI, c = cobicistat; CrCl = creatine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate glucuronosyltransferase

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Dolutegravir (DTG) *Tivicay* **Also available as a component of a fixed-dose combination (by trade name and abbreviation):**	• 50 mg tablet	ARV-Naive or ARV-Experienced, INSTI-Naive Patients: • 50 mg once daily ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Coadministered with EFV, FPV/r, TPV/r, or Rifampin: • 50 mg BID INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance: • 50 mg BID Take without regard to meals.	UGT1A1-mediated glucuronidation Minor contribution from CYP3A4	~14 hours	• HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported. • Insomnia • Headache • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
Triumeq (DTG/ABC/3TC)	Triumeq: • (DTG 50 mg + ABC 600 mg + 3TC 300 mg) tablet	Triumeq: • Take 1 tablet daily without regard to meals.			
Elvitegravir (EVG) **Only available as a component of fixed-dose combinations (by trade name and abbreviation):**	See fixed-dose combinations below.	See fixed-dose combinations below.	CYP3A, UGT1A1/3 substrate	~9 hours	• Nausea • Diarrhea • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
Genvoya (EVG/c/FTC/ TAF)	Genvoya: • (EVG 150 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food **Not recommended** for patients with CrCl <30 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	EVG: As above COBI: CYP3A, CYP2D6 (minor) substrate; CYP3A inhibitor	~13 hours	
Stribild (EVG/c/FTC/ TDF)	Stribild: • (EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).		~13 hours	

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Raltegravir (RAL) *Isentress* *Isentress HD*	• 400 mg tablet • 600 mg tablet (HD) • 25 and 100 mg chewable tablets • 100 mg single packet for oral suspension	ARV-Naive Patients or ARV-Experienced Patients: • Isentress: 400 mg BID ARV-Naive or ARV-Experienced Patients who are Virologically Suppressed on a Regimen of RAL 400 mg BID: • Isentress HD: 1200 mg (two 600-mg tablets) once daily With Rifampin: • Isentress: 800 mg BID • Isentress HD: Not recommended Take without regard to meals.	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 • Insomnia • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BID = twice daily; COBI, c = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; UGT = uridine diphosphate glucuronosyltransferase

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Last updated January 29, 2008; last reviewed October 17, 2017)

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Storage	Adverse Events[a]
Enfuvirtide (T20) *Fuzeon*	• Injectable; supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.	• 90 mg (1 mL) subcutaneously BID	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.	Store at room temperature (up to 25° C or 77° F). Reconstituted solution should be refrigerated at 2° to 8° C (36° to 46° F) and used within 24 hours.	• Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) occur in almost 100% of patients • Increased incidence of bacterial pneumonia • HSR (<1% of patients). Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge **is not recommended**.

[a] Also see Table 14.

Key to Abbreviations: BID = twice daily; HSR = hypersensitivity reaction; T20 = enfuvirtide

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed October 17, 2017)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	• 150 and 300 mg tablets	• **150 mg BID** when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, T20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals.	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 dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 17, 2017; last reviewed October 17, 2017) (page 1 of 6)

See the reference section at the end of this table for CrCl calculation formulas and criteria for Child-Pugh classification.

<table>
<tr><th>Generic Name
(Abbreviation)
Trade Name</th><th>Usual Daily Dose[a]</th><th>Dosing in Renal Insufficiency[b]</th><th>Dosing in Hepatic Impairment</th></tr>
<tr><td colspan="4">NRTIs
Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations <u>is not recommended</u> in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Epzicom, Triumeq, or Trizivir. Descovy, Genvoya, Odefsey, and Truvada <u>are not recommended</u> in patients with CrCl <30 mL/min.</td></tr>
<tr><td>Abacavir
(ABC)
Ziagen</td><td>• 300 mg PO BID</td><td>No dosage adjustment necessary</td><td><u>Child-Pugh Class A</u>:
• 200 mg PO BID (use oral solution)
<u>Child-Pugh Class B or C</u>:
• Contraindicated</td></tr>
<tr><td>Didanosine EC
(ddI)
Videx EC</td><td><u>Body Weight ≥60 kg</u>:
• 400 mg PO once daily
<u>Body Weight <60 kg</u>:
• 250 mg PO once daily</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>125 mg</td></tr><tr><td>10–29</td><td>125 mg</td><td>125 mg</td></tr><tr><td><10, HD,[c] CAPD</td><td>125 mg</td><td>75 mg oral solution</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Didanosine Oral Solution
(ddI)
Videx</td><td><u>Body Weight ≥60 kg</u>:
• 200 mg PO BID, or
• 400 mg PO once daily
<u>Body Weight <60 kg</u>:
• 250 mg PO once daily, or
• 125 mg PO BID</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>150 mg</td></tr><tr><td>10–29</td><td>150 mg</td><td>100 mg</td></tr><tr><td><10, HD,[c] CAPD</td><td>100 mg</td><td>75 mg</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>• 200 mg oral capsule once daily, or
• 240 mg (24 mL) oral solution once daily</td><td><table><tr><th colspan="3">Dose</th></tr><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg q48h</td><td>120 mg q24h</td></tr><tr><td>15–29</td><td>200 mg q72h</td><td>80 mg q24h</td></tr><tr><td><15 or on HD[c]</td><td>200 mg q96h</td><td>60 mg q24h</td></tr></table></td><td>No dosage recommendation</td></tr>
<tr><td>Lamivudine
(3TC)
Epivir</td><td>• 300 mg PO once daily, or
• 150 mg PO BID</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>150 mg q24h</td></tr><tr><td>15–29</td><td>1 x 150 mg, then 100 mg q24h</td></tr><tr><td>5–14</td><td>1 x 150 mg, then 50 mg q24h</td></tr><tr><td><5 or on HD[c]</td><td>1 x 50 mg, then 25 mg q24h</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Stavudine
(d4T)
Zerit</td><td><u>Body Weight ≥60 kg</u>:
• 40 mg PO BID
<u>Body Weight <60 kg</u>:
• 30 mg PO BID</td><td><table><tr><th colspan="3">Dose</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>26–50</td><td>20 mg q12h</td><td>15 mg q12h</td></tr><tr><td>10–25 or on HD[c]</td><td>20 mg q24h</td><td>15 mg q24h</td></tr></table></td><td>No dosage recommendation</td></tr>
</table>

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 17, 2017; last reviewed October 17, 2017) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NRTIs, continued			
Tenofovir Alafenamide/ Emtricitabine (TAF/FTC) *Descovy*	TAF available as a component of fixed-dose combinations for HIV (i.e., Descovy, Genvoya, and Odefsey) • TAF 10 mg PO daily with EVG/c (Genvoya), *or* • TAF 25 mg PO daily in other fixed-dose combinations	**CrCl (ml/min)** / **Dose** <30 or on HD[c] / Not recommended	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Tenofovir Disoproxil Fumarate (TDF) *Viread*	• 300 mg PO once daily	**CrCl (mL/min)** / **Dose** 30–49 / 300 mg q48h 10–29 / 300 mg twice weekly (every 72–96 hours) <10 and not on HD / No recommendation On HD[c] / 300 mg q7d	No dosage adjustment necessary
Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) *Truvada*	• 1 tablet PO once daily	**CrCl (mL/min)** / **Dose** 30–49 / 1 tablet q48h <30 or on HD / Not recommended	No dosage recommendation
Zidovudine (ZDV) *Retrovir*	• 300 mg PO BID	**CrCl (mL/min)** / **Dose** <15 or on HD[c] / 100 mg TID or 300 mg once daily	No dosage recommendation
NNRTIs			
Efavirenz (EFV) *Sustiva*	• 600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	Child-Pugh Class A: • No dosage adjustment Child-Pugh Class B or C: • Not recommended
Efavirenz/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	• 1 tablet PO once daily	**Not recommended** for use in patients with CrCl <50 mL/min. Instead, use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	
Etravirine (ETR) *Intelence*	• 200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Nevirapine (NVP) *Viramune* *Viramune XR*	• 200 mg PO BID, *or* • 400 mg PO once daily (using Viramune XR formulation)	Patients on HD: • Limited data; no dosage recommendation	Child-Pugh Class A: • No dosage adjustment Child-Pugh Class B or C: • Contraindicated

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 17, 2017; last reviewed October 17, 2017) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NNRTIs, continued			
Rilpivirine (RPV) *Edurant*	• 25 mg PO once daily	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine/ Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) *Odefsey*	• 1 tablet PO once daily	**Not recommended** for use in patients with CrCl <30 mL/min	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine/ Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) *Complera*	• 1 tablet PO once daily	**Not recommended** for use in patients with CrCl <50 mL/min. Instead, use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
PIs			
Atazanavir (ATV) *Reyataz*	• 400 mg PO once daily, *or* • (ATV 300 mg + RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction who do not require HD. ARV-Naive Patients on HD: • (ATV 300 mg + RTV 100 mg) once daily ARV-Experienced Patients on HD: • ATV or ATV/r not recommended.	Child-Pugh Class B: • 300 mg once daily Child-Pugh Class C: • Not recommended RTV boosting **is not recommended** in patients with hepatic impairment.
Atazanavir/ Cobicistat (ATV/c) *Evotaz*	• 1 tablet PO once daily	If Used with TDF: • Not recommended for use in patients with CrCl <70 mL/min	**Not recommended** in patients with hepatic impairment
Darunavir (DRV) *Prezista*	ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations: • (DRV 800 mg + RTV 100 mg) PO once daily ARV-Experienced Patients with at Least 1 DRV Resistance Mutation: • (DRV 600 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • No dosage adjustment Severe Hepatic Impairment: • Not recommended

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 17, 2017; last reviewed October 17, 2017) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
PIs, continued			
Darunavir/ Cobicistat (DRV/c) *Prezcobix*	• 1 tablet PO once daily (only recommended for patients without DRV-associated resistance mutations)	If Used with TDF: • Not recommended for use in patients with CrCl <70 mL/min	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Fosamprenavir (FPV) *Lexiva*	• 1400 mg PO BID, *or* • (FPV 1400 mg + RTV 100–200 mg) PO once daily, *or* • (FPV 700 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	PI-Naive Patients Only *Child-Pugh Score 5–9:* • 700 mg BID *Child-Pugh Score 10–15:* • 350 mg BID PI-Naive or PI-Experienced Patients *Child-Pugh Score 5–6:* • (700 mg BID + RTV 100 mg) once daily *Child-Pugh Score 7–9:* • (450 mg BID + RTV 100 mg) once daily *Child-Pugh Score 10–15:* • (300 mg BID + RTV 100 mg) once daily
Indinavir (IDV) *Crixivan*	• 800 mg PO q8h	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency Because of Cirrhosis: • 600 mg q8h
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	• (LPV 400 mg + RTV 100 mg) PO BID, *or* • (LPV 800 mg + RTV 200 mg) PO once daily	Avoid once-daily dosing in patients on HD	No dosage recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV) *Viracept*	• 1250 mg PO BID	No dosage adjustment necessary	Mild Hepatic Impairment: • No dosage adjustment Moderate-to-Severe Hepatic Impairment: • Do not use
Ritonavir (RTV) *Norvir*	As a PI-Boosting Agent: • 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV) *Invirase*	• (SQV 1000 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • Use with caution Severe Hepatic Impairment: • Contraindicated

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 17, 2017; last reviewed October 17, 2017) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
PIs, continued			
Tipranavir (TPV) *Aptivus*	• (TPV 500 mg + RTV 200 mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: • Use with caution Child-Pugh Class B or C: • Contraindicated
INSTIs			
Dolutegravir (DTG) *Tivicay*	• 50 mg once daily, *or* • 50 mg BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Elvitegravir/ Cobicistat/ Tenofovir Alafenamide/ Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	• 1 tablet once daily	Not recommended for use in patients with CrCl <30 mL/min.	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended
Elvitegravir/ Cobicistat/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EVG/c/TDF/FTC) *Stribild*	• 1 tablet 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.	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended
Raltegravir (RAL) *Isentress* *Isentress HD*	• 400 mg BID (using Isentress formulation), *or* • 1200 mg once daily (use Isentress HD formulation only) Do not substitute Isentress tablets for Isentress HD dosage.	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • No recommendation
Fusion Inhibitor			
Enfuvirtide (T20) *Fuzeon*	• 90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	• The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 6 for detailed dosing information.	CrCl <30 mL/min or on HD: *Without Potent CYP3A Inhibitors or Inducers:* • 300 mg BID; reduce to 150 mg BID if postural hypotension occurs. *With Potent CYP3A Inducers or Inhibitors:* • Not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 17, 2017; last reviewed October 17, 2017) (page 6 of 6)

[a] Refer to Appendix B, Tables 1–6 for additional dosing information.

[b] Including with chronic ambulatory peritoneal dialysis and hemodialysis.

[c] On dialysis days, take dose after HD session.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AZT = zidovudine; BID = twice daily; COBI, c = cobicistat; CAPD = chronic ambulatory peritoneal dialysis; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IDV = indinavir; 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 = orally; q(n)d = every (n) days; q(n)h = every (n) hours; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZDV = zidovudine

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 µmol/L to 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 used for patients who have Gilbert's syndrome or who are taking indinavir or 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