



Complete Summary

GUIDELINE TITLE

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.

BIBLIOGRAPHIC SOURCE(S)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2008 Nov 3. 139 p. [558 references]

GUIDELINE STATUS

This is the current release of the guideline. It was last updated on November 3, 2008.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines, therefore, are updated frequently by the Panel and are available as a "living document" at the <http://www.aidsinfo.nih.gov> Web site.

Status information regarding this guideline is available from the [AIDSinfo Web site](#), telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [July 24, 2008, Ziagen \(abacavir sulfate\)](#): The U.S. Food and Drug Administration (FDA) has notified the maker of abacavir and abacavir-containing medications of the need to add information to the current BOXED WARNING about the recommendation to test all patients for the HLA-B*5701 allele before starting or restarting therapy with abacavir or abacavir-containing medications.
- [March 12, 2008, Prezista \(darunavir\)](#): The U.S. Food and Drug Administration (FDA) and Tibotec Therapeutics notified healthcare professionals of changes to the WARNINGS section of the prescribing information for Prezista (darunavir) tablets regarding the risk of hepatotoxicity, specifically, drug

induced hepatitis in patients receiving combination therapy with Prezista/ritonavir.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

IDENTIFYING INFORMATION AND AVAILABILITY

DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infections (including asymptomatic, established, and acute HIV)
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Counseling
Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To update the January 2008 guidelines

- To provide guidance to human immunodeficiency virus (HIV) care practitioners on the optimal use of antiretroviral agents for the treatment of HIV infection in adults and adolescents in the United States

TARGET POPULATION

Adults and adolescents infected with human immunodeficiency virus (HIV)

These guidelines focus on treatment for adults and adolescents. Separate guidelines outline the use of antiretroviral therapy for such populations as pregnant women, children, and those who experience occupational and nonoccupational exposure to HIV. There is a brief discussion of the management of women in reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise offered by panels that have developed these guidelines.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Baseline evaluation
 - Medical history, physical examination
 - Laboratory tests, including human immunodeficiency virus antibody, CD4 cell count, plasma human immunodeficiency virus (HIV) ribonucleic acid (RNA), and other tests, as indicated
2. Initial assessment and monitoring for therapeutic response
 - CD4 counts
 - Plasma HIV RNA testing (Viral load)
 - Drug resistance testing
 - HLA-B*5701 screening
 - Coreceptor tropism assays
3. Initial regimens for the antiretroviral-naïve patient
 - Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (1 NNRTI + 2 nucleoside reverse transcriptase inhibitors [NRTI])
 - Preferred NNRTI
 - Alternative NNRTI
 - Protease inhibitor (PI)-based regimens (ritonavir-boosted or unboosted PI + 2 NRTIs)
 - Preferred PI
 - Alternative PI
 - Dual nucleoside options as part of initial combination therapy
 - Preferred dual-NRTI
 - Alternative dual-NRTI
4. Managing treatment-experienced patients
 - Assessment of treatment failure
 - Changing antiretroviral therapy
 - Regimen simplification
 - Therapeutic drug monitoring
 - Discontinuation or interruption of antiretroviral therapy
5. Considerations for antiretroviral use in special populations
 - Acute HIV infection

- HIV-infected adolescents
- Injection drug users
- HIV-infected women of reproductive age and pregnant women
- Patients with co-infections (hepatitis B, hepatitis C, *Mycobacterium tuberculosis*)

6. Prevention counseling

MAJOR OUTCOMES CONSIDERED

- Viral load
- Immunologic function
- Adherence to treatment
- Therapy-associated adverse effects
- Quality of life
- Human immunodeficiency virus (HIV)-related morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
 Searches of Electronic Databases
 Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Evidence Collection

The recommendations generally 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 U.S. Food and Drug Administration (FDA) and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

- I. One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
- II. One or more well designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III. Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Department of Health and Human Services (DHHS) 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 recommendations for HIV practitioners based on current knowledge of antiretroviral drugs used to treat adults and adolescents with HIV infection in the United States. The Panel reviews new evidence and updates recommendations when needed. The primary areas of attention have included baseline assessment, treatment goals, indications for initiation of antiretroviral therapy, choice of the initial regimen in treatment-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug interactions, management of treatment failure, and special considerations in specific patient populations.

Method of Synthesizing Data

Each section of the guidelines is assigned to a working group with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.

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), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the <http://www.aidsinfo.nih.gov> Web site.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

- A. Strong recommendation for the statement
- B. Moderate recommendation for the statement
- C. Optional recommendation

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After release of an update in the *AIDSinfo* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether or not revisions are indicated. The public is also able to submit comments to the Panel at aidsinfowebmaster@aidsinfo.nih.gov.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations usually are followed by levels of evidence (I-III) identifying the type of supporting evidence and strength of recommendation grades (A-C). Definitions for these are presented at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC) and the Department of Health and Human Services: *These guidelines were updated by the developer on November 3, 2008. Following are the major changes that have been made to the January 29, 2008 version of the guidelines, followed by the guideline recommendations. Please refer to the original guideline document at <http://www.aidsinfo.nih.gov> for further details.*

What's New in the Document?

The following changes have been made to the January 29, 2008 version of the guidelines:

Format Changes

This revision is developed under a new format, whereby the relevant tables and references for each section are incorporated into the body of the document. Some larger tables are placed in an appendix at the end of the document. A separate PDF file with all the tables can be found at the *AIDSinfo* Web site.

Rating Changes

A new rating scheme is used in this guideline to be more consistent with other guidelines in infectious diseases. The changes are outlined below:

Strength of Recommendations

The **D** (should usually not be offered) and **E** (should never be offered) ratings have been removed. The **A**, **B**, and **C** ratings rate the strength of the statement. For example, an **A** rating for "not to initiate nevirapine in women with pre-treatment CD4 cell count >250 cells/mm³" indicates a strong recommendation to not initiate nevirapine in these patients.

Quality of Evidence

Previously, only randomized trials with clinical endpoints were given a **I** ranking. In this new rating scheme, a **I** ranking includes randomized trials with either clinical or validated laboratory outcomes (e.g., viral load). A **II** rating includes non-randomized trials or well-designed observational cohort studies with long term clinical outcomes. A **III** rating remains a recommendation based on expert opinion.

Content Changes

The key changes to the different sections of the guidelines are outline below:

Laboratory Monitoring

- A new table (Table 3) provides recommendations for laboratory tests to obtain at baseline and while receiving antiretroviral therapy to monitor for safety and treatment responses.
- The Panel recommends that resistance testing be considered in patients with viral loads of 500 to 1,000 copies/mL but recognizes that it may not always be reliable at those levels (**BII**).

What to Start in Antiretroviral-Naïve Patients

Protease Inhibitor (PI)-Based Regimens

- Ritonavir-boosted darunavir has been added as a preferred PI component (**AI**).
- Once-daily ritonavir-boosted lopinavir has been moved from alternative to preferred PI component (except for pregnant women) (**AI**).

Dual-Nucleoside Reverse Transcriptase Inhibitor (NRTI) Options

- Abacavir + lamivudine has been moved from a preferred to an alternative dual-NRTI component because of concerns regarding an increased risk of myocardial infarction in patients with high cardiac risk factors, as suggested by large observational cohort studies, and concerns regarding virologic potency in patients with baseline viral loads >100,000 copies/mL (**BI**).

Combinations Not to Use or to Use with Caution

- A combination of unboosted atazanavir + didanosine + emtricitabine (or lamivudine) is not recommended because of efficacy concerns **(BI)**.
- A combination of nevirapine + tenofovir + emtricitabine (or lamivudine) should be used with caution and with close monitoring of virologic responses because of reports of early virologic failure with several small studies **(CII)**.

Management of Treatment-Experienced Patients

Regimen Simplification

- A new section on Regimen Simplification for virologically suppressed patients has been added to the discussion of Management of the Treatment-Experienced Patient.

Additional Updates

The following sections and their relevant tables have been updated:

- Introduction
- CD4+ T-cell count
- Viral Load Testing
- Coreceptor Tropism Assay
- What Not to Use
- Exposure Response and Therapeutic Drug Monitoring (and table for recommended antiretroviral drug concentrations)
- Human Immunodeficiency Virus (HIV)-Infected Adolescents
- HIV-Infected Illicit Drug Users
- HIV-Infected Women
- Adherence to Antiretroviral Therapy (with a new table)
- Antiretroviral-Associated Adverse Effects (and table for detection and management of adverse effects)
- Antiretroviral Drug Interactions (with a new format for interactions between antiretroviral and other drugs)
- Tables describing the characteristics of antiretroviral drugs

Baseline Evaluation

Each HIV-infected patient initially entering into care should have a complete medical history, physical examination, laboratory evaluation, and counseling. The purpose is to confirm the presence of HIV infection, obtain appropriate baseline historical and laboratory data, assure patient understanding about HIV infection, and initiate care as recommended by the HIV primary care guidelines and by the opportunistic treatment and prevention guidelines. Baseline information then is used to define management goals and plans.

The following laboratory tests should be performed for a new patient during initial patient visits:

- HIV antibody testing (if primary documentation not available) or if HIV ribonucleic acid (RNA) is undetectable **(AI)**
- CD4 T-cell count **(AI)**
- Plasma HIV RNA (viral load) **(AI)**
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN) and creatinine, urinalysis, screening test for syphilis (e.g., Rapid Plasma Reagin [RPR], Venereal Disease Research Laboratory [VDRL], or treponema enzyme immunoassay [EIA]), tuberculin skin test (TST) or interferon-gamma release assay (IGRA) (unless there is a history of prior tuberculosis or positive TST or IGRA), anti-*Toxoplasma gondii* immunoglobulin G (IgG), hepatitis A, B, and C serologies, and Pap smear in women **(AIII)**
- Fasting blood glucose and serum lipids if considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy **(AIII)**
- For patients with pretreatment HIV RNA >1,000 copies/mL, genotypic resistance testing when the patients enter into care, regardless of whether therapy will be initiated immediately **(AIII)**. For patients who have HIV RNA levels of 500 to 1,000 copies/mL, resistance testing also may be considered, even though amplification may not always be successful **(BII)**. If therapy is to be deferred, repeat testing at the time of antiretroviral initiation should be considered. **(CIII)** (See "Drug Resistance Testing" section below.)

In addition:

- Testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is encouraged to identify both recent high risk sexual behavior and the need for sexually transmitted disease (STD) therapy **(BII)**
- Chest x-ray in the presence of pulmonary symptoms or with a positive TST or IGRA test **(BIII)**

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues that are best addressed through a multidisciplinary approach to the disease. The evaluation should also include assessment of substance abuse, economic factors, (e.g., unstable housing), social support, mental illness, comorbidities, high-risk behaviors, and other factors that are known to impair the ability to adhere to treatment and to promote HIV transmission. Once evaluated, these factors should be managed accordingly.

Lastly, education about HIV risk behaviors and effective strategies to prevent HIV transmission to others should be provided at each patient clinic visit.

Laboratory Testing for Initial Assessment and Monitoring for Treatment Responses

A number of laboratory evaluations are important for initial assessment in HIV-1 infected patients upon entry into care, during follow-up if therapy is not yet initiated, and prior to and after initiation of therapy to assess virologic and immunologic efficacy of antiretroviral therapy and to monitor for laboratory abnormalities that may be associated with antiretroviral drugs. Table 3 in the original guideline document outlines the Panel's recommendations for the frequency of testing. As noted in the table, some of the tests may be repeated more frequently if clinically indicated.

CD4 T-Cell Count

Use of CD4 Count for Initial Assessment

The CD4 count is usually the most important consideration in decisions to initiate antiretroviral therapy and/or prophylaxis for opportunistic infections. All patients should have a baseline CD4 cell count at entry into care **(AI)**. Recommendations for initiation of antiretroviral therapy based on CD4 count are found below in the "When to Start: Indications for Initiation of Antiretroviral Therapy" section.

Use of CD4 Count for Monitoring Therapeutic Response

An adequate CD4 response for most patients on therapy is defined as an increase in CD4 count in the range of 50 to 150 cells/mm³ per year with an accelerated response in the first three months. Subsequent increases in patients with good virologic control show an average increase of approximately 50 to 100 cells/mm³ per year for the subsequent years until a steady state level is reached. Some patients who initiate therapy with a severely depleted CD4 count may have a blunted increase in their count despite virologic suppression.

Frequency of CD4 T-Cell Count Monitoring

In general, CD4 count should be determined every three to four months to (1) determine when to start antiretroviral therapy in patients not being treated; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiation or discontinuation of prophylaxis for opportunistic infections **(AI)**. For those patients who are adherent to therapy with sustained viral suppression and stable clinical status for more than 2 to 3 years, the frequency of CD4 count monitoring may be extended to every 6 months **(BIII)**.

Plasma HIV RNA Testing

Plasma HIV RNA (viral load) should be measured in all patients at baseline and on a regular basis thereafter, especially in patients who are on treatment, as viral load is the most important indicator of response to antiretroviral therapy **(AI)**.

One key goal of therapy is suppression of viral load to below the limits of detection (below 40 to 75 copies/mL by most commercially available assays). For most individuals who are adherent to their antiretroviral regimens and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 16 to 24 weeks, even though it may take a longer time in some patients. Recommendations for the frequency of viral load monitoring are summarized below.

At Initiation or Change in Therapy

Plasma viral load should be measured before initiation of therapy and preferably within 2 to 4 weeks, and not more than 8 weeks, after treatment initiation or after treatment modification **(BI)**. Repeat viral load measurement should be performed at 4 to 8 week intervals until the level falls below the assay's limit of detection **(BII)**.

In Patients Who Have Viral Suppression but Therapy Was Modified Due to Drug Toxicity or Regimen Simplification

Viral load measurement should be performed within 2 to 8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen **(BII)**.

In Patients on a Stable Antiretroviral Regimen

Viral load should be repeated every 3 to 4 months or as clinically indicated **(BII)**. In adherent patients who have suppressed viral loads for more than 2 to 3 years and who are at stable clinical and immunologic status, some clinicians may extend the interval to every 6 months **(BIII)**.

Monitoring in Patients with Suboptimal Response

In addition to viral load monitoring, a number of additional factors should be assessed, such as nonadherence, altered pharmacology, or drug interactions. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen, as discussed in the "Drug Resistance Testing" section, below **(AII)**.

Drug Resistance Testing

Panel's Recommendations

- HIV drug resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately **(AIII)**. If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered **(CIII)**.
- A genotypic assay is generally preferred for antiretroviral-naïve persons **(AIII)**.
- HIV drug resistance testing should be performed to assist in selection of active drugs when changing antiretroviral regimens in cases of virologic failure and HIV RNA levels >1,000 copies/mL **(AII)**. In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.
- Drug resistance testing should also be performed when managing suboptimal viral load reduction **(AII)**.
- Drug resistance testing in the setting of virologic failure should be performed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy **(AII)**.
- Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**.

See Table 4 in the original guideline document for recommendations and rationale regarding drug-resistance assays.

HLA-B*5701 Screening

Panel's Recommendations

- The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen, to reduce the risk of hypersensitivity reaction **(AI)**.
- HLA-B*5701-positive patients should not be prescribed abacavir **(AI)**.
- The positive status should be recorded as an abacavir allergy in the patient's medical record **(AII)**.
- When HLA-B*5701 screening is not readily available, it remains reasonable to initiate abacavir with appropriate clinical counseling and monitoring for any signs of hypersensitivity reaction **(CIII)**.

Coreceptor Tropism Assays

Panel's Recommendations

- Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered **(AII)**.
- Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor **(BIII)**.

Treatment Goals

The primary goals driving the decision to initiate antiretroviral therapy are to:

- Reduce HIV-related morbidity and prolong survival
- Improve quality of life
- Restore and preserve immunologic functions
- Maximally and durably suppress viral load
- Prevent vertical HIV transmission

Strategies to Achieve Treatment Goals

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define priorities and determine treatment goals and options. See the original guideline document for more information on these topics.

- Selection of Initial Combination Regimen
- Pretreatment Drug Resistance Testing
- Improving Adherence

When to Start: Indications for Initiation of Antiretroviral Therapy

Panel's Recommendations

- Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 T-cell count <350 cells/mm³. The data

supporting this recommendation are stronger for those with a CD4 T-cell count <200 cells/mm³ and with a history of AIDS **(AI)** than for those with CD4 T-cell counts between 200 and 350 cells/mm³ **(AII)**.

- Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count:
 - a. Pregnant women **(AI)**
 - b. Patients with HIV-associated nephropathy **(AI)**
 - c. Patients coinfecting with HBV when treatment for HBV infection is indicated **(BIII)**
- Antiretroviral therapy may be considered in some patients with CD4 T-cell counts >350 cells/mm³. (See original guideline document for further discussion.)
- The necessity for patient adherence to a long-term drug regimen should be discussed in depth by the patient and clinician **(AIII)**. Potential barriers to adherence should be addressed before therapy is initiated.

Before initiating therapy, patient counseling and education should be conducted. The patient should understand the potential benefits and risks of antiretroviral therapy, including short- and long-term adverse drug effects and the need for long-term commitment and adherence to the prescribed treatment regimen.

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient

Summary of Recommended Regimens

The most extensively studied combination antiretroviral regimens for treatment-naïve patients generally consist of two NRTIs plus either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI (with or without ritonavir-boosting). A list of Panel-recommended components for initial therapy in treatment-naïve patients can be found in Table 6 of the original guideline document. Potential advantages and disadvantages of the components recommended as initial therapy for treatment-naïve patients are listed in Table 7 of the original guideline document to guide prescribers in choosing the regimen best suited for an individual patient. A list of agents or components not recommended for initial treatment can be found in Table 8 of the original guideline document. Some agents or components not generally recommended for use because of lack of potency or potential serious safety concerns are listed in Table 9 of the original guideline document.

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized and should consider a number of factors including:

- Comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis)
- Potential adverse drug effects
- Potential drug interactions with other medications
- Pregnancy or pregnancy potential

- Results of genotypic drug resistance testing
- Gender and pretreatment CD4 T-cell count if considering nevirapine
- HLA B*5701 testing if considering abacavir
- Patient adherence potential
- Convenience (e.g., pill burden, dosing frequency, and food and fluid considerations)

NNRTI-Based Regimens (1 NNRTI + 2 NRTIs)

Panel's Recommendations

Preferred NNRTI (AI):

- Efavirenz (except during first trimester of pregnancy or in women with high pregnancy potential*)

Alternative NNRTI (BI):

- Nevirapine may be used as an alternative in adult females with CD4 T-cell counts ≤ 250 cells/mm³ and adult males with CD4 T-cell counts ≤ 400 cells/mm³

*Women of child bearing age with high pregnancy potential are those who are trying to conceive or who are sexually active with men and not using effective and consistent contraception.

PI-Based Regimens (Ritonavir-Boosted or Unboosted PI + 2 NRTIs)

Panel's Recommendations

Preferred PI (in alphabetical order):

- Atazanavir + ritonavir once daily (AI)
- Darunavir + ritonavir once daily (AI)
- Fosamprenavir + ritonavir twice-daily (BI)
- Lopinavir/ritonavir (co-formulated) once or twice daily (AI)

Alternative PI (BI) (in alphabetical order):

- Atazanavir* (unboosted) once daily
- Fosamprenavir (unboosted) twice daily
- Fosamprenavir + ritonavir once daily
- Saquinavir + ritonavir twice daily

* Ritonavir 100 mg per day must be given when tenofovir or efavirenz is used with atazanavir

Dual-Nucleoside Options as Part of Initial Combination Therapy

Panel's Recommendations

Preferred Dual-NRTI (AI):

- Tenofovir/emtricitabine* (co-formulated)

Alternative Dual-NRTIs (BI) (in alphabetical order):

- Abacavir/lamivudine* (co-formulated) in patients tested negative of HLA-B*5701
- Didanosine + (lamivudine or emtricitabine)
- Zidovudine/lamivudine* (co-formulated)

*Emtricitabine may be used in place of lamivudine or vice versa.

All-NRTI Regimens

A triple-NRTI combination regimen has multiple potential advantages: fewer drug-drug interactions (e.g., none with rifampin), low pill burden, availability of a fixed-dose combination (e.g., zidovudine/lamivudine/abacavir), and the ability to spare patients from potential adverse effects seen with PIs and NNRTIs. However, several clinical trials that studied triple-NRTI regimens have shown suboptimal virologic activity, and current PI- and NNRTI-based regimens have improved convenience and tolerability compared with older regimens.

Abacavir/Lamivudine/Zidovudine (co-formulated)

Abacavir/lamivudine/zidovudine is the only triple-NRTI combination for which randomized, controlled trials are available. Abacavir/lamivudine/zidovudine demonstrated comparable antiretroviral activity to indinavir-based and nelfinavir-based but was inferior virologically to an efavirenz-based regimen. This combination is **generally not recommended (BI)** and should be used only when a preferred or an alternative NNRTI-based or a PI-based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.

Zidovudine/Lamivudine + Tenofovir

The DART study demonstrated that the combination of zidovudine/lamivudine + tenofovir has antiviral activity; however, comparative data with standard regimens are not available and therefore **cannot be recommended** in routine clinical practice (**BIII**).

A quadruple-NRTI regimen of zidovudine + lamivudine + abacavir + tenofovir showed comparable virologic responses to an efavirenz-based regimen in a small pilot study, but definitive data are lacking. Thus, this regimen **cannot be recommended** at this time (**BII**).

Other Treatment Options under Investigation: Insufficient Data to Recommend

Several novel treatment regimens that use agents approved for treatment-experienced patients are currently in Phase II or III clinical trials, evaluating their safety and efficacy in treatment-naïve patients. Preliminary data from these trials are summarized in the original guideline document for the following:

- Raltegravir-based regimen
- Maraviroc-based regimen

What Not to Use: (See Table 9 in the original guideline document)

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

Antiretroviral Regimens Not Recommended

Monotherapy with NRTI

Single-NRTI therapy does not demonstrate potent and sustained antiviral activity and **should not be used (AII)**. For prevention of mother-to-child transmission, zidovudine monotherapy might be considered in certain unusual circumstances in women with HIV RNA <1,000 copies/mL. Even then, the use of a potent combination regimen is generally recommended. See the NGC summary: [Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#).

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir or atazanavir, are under investigation but cannot be recommended outside of a clinical trial at this time.

Dual Nucleoside Regimens

These regimens are not recommended because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens. **(AI)**

Triple-NRTI Regimens

Except for abacavir/lamivudine/zidovudine and possibly zidovudine/lamivudine + tenofovir, triple-NRTI regimens should NOT be used routinely because of suboptimal virologic activity or lack of data. **(AI)**

Antiretroviral Components Not Recommended (in alphabetical order) (See the original guideline document for more information on these components.)

- Atazanavir + Indinavir **(AIII)**
- Didanosine + Stavudine **(AII)**
- Two-NNRTI Combination **(AI)**
- Efavirenz in First Trimester of Pregnancy and in Women with Significant Childbearing Potential **(AIII)**

- Emtricitabine + Lamivudine **(AIII)**
- Etravirine + Unboosted PI **(AII)**
- Etravirine + Ritonavir-Boosted Atazanavir, Fosamprenavir, or Tipranavir **(AII)**
- Nevirapine Initiated in Treatment-naïve Women with CD4 Counts >250 cells/mm³ or in Treatment-naïve Men with CD4 Counts >400 cells/mm³ **(BI)**
- Unboosted Darunavir, Saquinavir, or Tipranavir **(AII)**
- Stavudine + Zidovudine **(AII)**

Management of the Treatment-Experienced Patient

Panel's Recommendations

- In treatment-experienced patients with suppressed viremia, assess adherence frequently and simplify the regimen as much as possible. Change individual antiretroviral drugs to reduce or manage toxicity, as needed.
- Evaluation of antiretroviral treatment failure in a patient should include an assessment of the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; HIV RNA and CD4 T-cell count trends over time; and the results of prior drug resistance testing.
- Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a repeated detectable HIV RNA level after prior suppression of viremia.
- Drug resistance testing should be obtained while the patient is taking the failing antiretroviral regimen (or within 4 weeks of treatment discontinuation) **(AI)**.
- The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, HIV RNA <50 copies/mL **(AI)**.
- Use the treatment history and the past and current resistance test results to identify fully active agents to design a new regimen **(AII)**. A fully active agent is one that is likely to have antiretroviral activity on the basis of both the treatment history and susceptibility on drug resistance testing. Adding at least two (preferably three) fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity **(BII)**.
- Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 response despite virologic suppression.
- For immunologic failure, current medications, untreated coinfection, and serious medical conditions should be assessed.
- There is no consensus for when and how to treat immunologic failure.
- Assessing and managing a patient who has antiretroviral experience, who exhibits drug resistance, and who is experiencing treatment failure is complex and expert advice is critical.

Management of Patients with Antiretroviral Treatment Failure

Definitions and Causes of Antiretroviral Treatment Failure

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression. Many factors are associated with an increased risk of treatment failure, including:

- Baseline patient factors such as:
 - Earlier calendar year of starting therapy, in which less potent regimens or less well-tolerated antiretroviral drugs were used
 - Higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
 - Lower pretreatment or nadir CD4 T-cell count
 - Prior AIDS diagnosis
 - Comorbidities (e.g., depression, active substance use)
 - Presence of drug-resistant virus
 - Prior treatment failure, with development of drug resistance or cross resistance
- Incomplete medication adherence and missed clinic appointments
- Drug side effects and toxicity
- Suboptimal pharmacokinetics (variable absorption, metabolism, and/or penetration into reservoirs, food/fasting requirements, adverse drug-drug interactions with concomitant medications)
- Suboptimal potency of the antiretroviral regimen
- Other, unknown reasons

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by:

- Reviewing the medical history including:
 - Change in HIV RNA and CD4 T-cell count over time
 - Occurrence of HIV-related clinical events
 - Antiretroviral treatment history
 - Results of prior resistance testing (if any)
 - Medication-taking behavior, including adherence to recommended drug doses, dosing frequency, and food/fasting requirements
 - Tolerability of the medications
 - Concomitant medications (with consideration for adverse drug-drug interactions)
 - Comorbidities (including substance use)
- Performing a physical examination to assess for signs of clinical progression

In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

Initial Assessment of Treatment Failure

In conducting the assessment of treatment failure, it is important to distinguish among the reasons for treatment failure because the approaches to subsequent treatment will differ. The following assessments should be undertaken initially:

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) for non-adherence

- (e.g., access to medications, depression, active substance use), and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) **(AIII)**. (See "Adherence" in the original guideline document).
- **Medication Intolerance.** Assess the patient's side effects. Address and review the likely duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance may include:
 - Using symptomatic treatment (e.g. antiemetics, antidiarrheals)
 - Changing one drug to another within the same drug class, if needed (e.g., change to tenofovir or abacavir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms) **(AII)**
 - Changing drug classes (e.g., from an NNRTI to a PI, from an injectable drug to an oral agent) if necessary **(AII)**
 - **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions and make appropriate substitutions for antiretroviral agents and/or concomitant medications, if possible **(AIII)**. (See also "Exposure Response Relationship and Therapeutic Drug Monitoring" in the original guideline document.)
 - **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation **(AII)** (see "Drug Resistance Testing" in the original guideline document).

Further Assessment of Treatment Failure

When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make an assessment for virologic failure, immunologic failure, and clinical progression.

Virologic suppression can be defined as a sustained reduction in HIV RNA level below the assay limit of detection (e.g., 50 copies/mL). Virologic failure is best understood in the context of virologic success; that is, virologic failure is defined as the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL) and may manifest as any of the following:

- **Incomplete virologic response:** Two consecutive HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient who is initiating therapy. Baseline HIV RNA may affect the time course of response, and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 log₁₀ decrease in HIV RNA copies/mL at 1 to 4 weeks after starting therapy.
- **Virologic rebound:** After virologic suppression, repeated detection of HIV RNA above the assay limit of detection (e.g., 50 copies/mL).

Assessment of Virologic Failure

There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >50 copies/mL after suppression to <50 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000 to 5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations and may limit future treatment options. Isolated episodes of viremia ("blips", e.g., single levels of 51 to 1,000 copies/mL) may simply represent laboratory variation and usually are not associated with subsequent virologic failure, but rebound to higher viral load levels or more frequent episodes of viremia increase the risk of failure.

When assessing virologic failure, one should assess the degree of drug resistance, and should take into account prior treatment history and prior resistance test results **(AII)**. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account.

Management of Virologic Failure

General Approach

Ideally, one should design a regimen with at least two, and preferably three, fully active drugs on the basis of drug history, resistance testing or new mechanistic class **(BII)**. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens. They included lower HIV RNA at the time of therapy change, using a new (i.e., not yet taken) class of drugs, and using ritonavir-boosted PIs in PI-experienced patients. More recent studies show that higher CD4 T-cell counts and higher genotypic and/or phenotypic susceptibility scores (indicating a greater number of active agents) are associated with better virologic responses.

In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 T-cell count <100/mm³) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and or transient increases in CD4 T-cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug in the heavily treatment-experienced patient is complicated, and consultation with an expert is advised.

Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA and a decrease in the CD4 T-cell count, and it

increases the risk for clinical progression. Therefore, it is not recommended **(BIII)**.

See the original guideline document for information on sequencing and cross resistance, and newer agents.

Clinical Scenarios in Management of Patients with Antiretroviral Treatment Failure

- **Prior treatment with no resistance identified.** Consider the timing of the drug resistance test (e.g., Was the patient off antiretroviral medications for >4 weeks?) and/or non-adherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2 to 4 weeks) to determine whether a resistant viral strain emerges **(CIII)**. Consider intensifying with one drug (e.g., tenofovir) **(BII)** or pharmacokinetic enhancement (ritonavir boosting of an unboosted PI, e.g., atazanavir, fosamprenavir) **(BII)**.
- **Prior treatment and drug resistance.** The goals in this situation are to resuppress HIV RNA levels maximally (e.g., to <50 copies/mL) and to prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Discontinuing an NNRTI in a patient with ongoing viremia and evidence of NNRTI resistance in order to decrease the risk of selecting additional NNRTI-resistance mutations is particularly important, because newer NNRTIs with activity against some NNRTI-resistant strains are available. A new regimen should include at least two, and preferably three, fully active agents **(BII)**.
- **Extensive prior treatment and drug resistance.** The goal is to resuppress the HIV RNA levels maximally (e.g., to <50 copies/mL). With the availability of multiple new antiretroviral drugs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. In some cases, however, viral suppression may be difficult to achieve. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 log₁₀ copies/mL from baseline correlates with clinical benefits; however, this must be balanced with the ongoing risk for accumulating additional resistance mutations.
- **New regimen that contains at least two fully active agents cannot be identified.** It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, decreases the risk of disease progression. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000 to 20,000 copies/mL.

Immunologic Failure

Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 T-cell response despite virologic suppression. There is no specific definition for immunologic failure, although some studies have focused on patients who fail to increase CD4 T-cell counts above a specific threshold (e.g., >350 or

500 cells/mm³) over a specific period of time (e.g., 4 to 7 years). Others have focused on an inability to increase CD4 T-cell counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm³) over a given time period. The former approach may be preferable because of recent data linking these thresholds with the risk of non-AIDS clinical events.

Factors Associated with Immunologic Failure

- CD4 count <200/mm³ when starting antiretroviral treatment (ART)
- Older age
- Coinfection (e.g., HCV)
- Medications, both antiretrovirals (zidovudine [ZDV], tenofovir [TDF] + didanosine [ddI]) and other medications
- Persistent immune activation
- Loss of regenerative potential of the immune system

Assessment of Immunologic Failure

CD4 T-cell count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., interferon, cancer chemotherapy, prednisone, zidovudine, combination of tenofovir and didanosine). Untreated coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure

There is no consensus on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 T-cell counts <200/mm³. Patients with higher CD4 T-cell counts have a low risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the antiretroviral drug regimen. Because ongoing viral replication occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However this strategy does not result in clear virologic or immunologic benefit. Others suggest changing the regimen (e.g., to a more suppressive regimen or from an NNRTI-based regimen to a PI-based regimen, based on some evidence that suggests improved CD4 T-cell count responses); however, these strategies have not been formally tested.

Immune-based therapies, such as interleukin-2, demonstrated robust and sustained CD4 T-cell count increases in some studies. However, controversy persists as to how much enhancement of immune function occurs. With this controversy, drug-associated side effects, and the need for parenteral administration, this strategy cannot be recommended unless with enrollment into a clinical trial (**BIII**). Other immune-based therapies (e.g., growth hormone, cyclosporine, interleukin-7) are currently under investigation. Currently, immune-based therapies should not be used unless in the context of a clinical trial (**BIII**).

Clinical Progression

Clinical progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression in 2.5 years.

Management of Clinical Progression

Consider the possibility of immune reconstitution syndrome, which typically occurs within the first 3 months after starting effective antiretroviral therapy and which may respond to anti-inflammatory treatment(s) rather than changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia and adequate immunologic response (**BIII**).

Relationship Among Virologic Failure, Immunologic Failure, and Clinical Progression

Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters. In addition, virologic failure, immunologic failure, and clinical progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years.

Regimen Simplification

Regimen simplification can be defined broadly as a change in established effective therapy to reduce pill burden and dosing frequency, to enhance tolerability, or to decrease specific food and fluid requirements. Many patients on suppressive antiretroviral therapy may be considered candidates for this strategy, especially if (1) they are receiving treatments that are no longer recommended as preferred or alternative choices for initial therapy, (2) if they were prescribed a regimen in the setting of treatment failure at a time when there was an incomplete understanding of resistance or drug-drug interaction data, or (3) if they were prescribed a regimen prior to the availability of newer options that might be easier to administer and/or more tolerable.

This section will review situations in which clinicians might consider simplifying treatment in a patient with virologic suppression. Importantly, this section will not be considering changes in treatment for reducing ongoing adverse effects. Regimens used in simplification strategies generally should be those that have proven high efficacy in treatment-naïve patients (See "What to Start" section, above.) or that would be predicted to be highly active for a given patient based on their past treatment history and resistance profile.

Refer to the original guideline document for a detailed discussion about rationale for regimen simplification, candidates for regimen simplification, types of treatment simplification, and monitoring after treatment simplification.

Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents

Panel's Recommendations

- Therapeutic drug monitoring (TDM) for antiretroviral agents is not recommended for routine use in the management of the HIV-infected adult **(CIII)**.

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes drug concentrations to design regimens that are safe and will achieve a desired therapeutic outcome. Refer to the original guideline document for a detailed discussion of this topic including:

- TDM with PIs and NNRTIs
- TDM with CCR5 antagonists
- DTM with integrase inhibitors
- TDM with NRTIs
- Scenarios for Use of TDM
- TDM in different patient populations (e.g., patients with drug-susceptible virus, treatment-experienced patients)
- Use of TDM to monitor drug concentrations

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 and patient information. In addition, as knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians employing a TDM strategy for patient management should consult the most current literature.

Discontinuation or Interruption of Antiretroviral Therapy

Short-term Therapy Interruptions

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

Unanticipated Need for Short-Term 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 Interruption (>2 to 3 Days)

- **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 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 is required to take nothing by mouth for a sustained period of 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 differing half-lives** -- stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically an NNRTI). Options in this circumstance are discussed below. (See "Discontinuation of efavirenz, etravirine, or nevirapine" below.)

Interruption of Therapy after Pregnancy

During pregnancy, HIV-infected pregnant women who otherwise do not meet current CD4 count or clinical criteria for starting treatment may initiate antiretroviral therapy primarily for the purpose of preventing mother-to-child HIV transmission. After delivery, these women may desire to stop therapy. Discontinuation recommendations are in the current guidelines for pregnant women and in the "HIV-Infected Women of Reproductive Age and Pregnant Women" section below.)

Planned Long-term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. None of the therapy interruptions can be recommended at this time outside of controlled clinical trials **(AI)**.

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression** -- the optimal duration of treatment and the consequences of treatment interruption are not known at this time. (See "Acute HIV Infection" section below.)
- **In patients who have had exposure to multiple antiretroviral agents, have experienced antiretroviral treatment failure, and have few treatment options available because of extensive resistance mutations** -- interruption is **not** recommended unless it is done in a clinical trial setting **(AI)**. Several clinical trials, largely yielding negative results, but some with conflicting results, have been conducted to better understand the role of treatment interruption in these patients. The largest of these studies showed negative clinical impact of treatment interruption in these patients. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit; therefore, interruption of therapy is not recommended.
- **In patients on antiretroviral therapy who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 count was either above or below that recommended threshold** -- interruption is also **not recommended** unless it is done in a clinical trial setting **(BI)**. (See the

original guideline document for discussion of potential adverse outcomes seen in some treatment interruption trials.)

Planned long-term therapy interruption strategies **cannot** be recommended at this time outside of controlled clinical trials (**BI**) based on available data and a range of ongoing concerns (see below).

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome, increased risk for HIV transmission, decline of CD4 cell count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of antiretroviral-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz, etravirine, or nevirapine.** The optimal interval between stopping efavirenz, etravirine, or nevirapine and other antiretroviral drugs is not known. The duration of detectable levels of these drugs after discontinuation ranges from less than one week to more than three weeks. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs, because their half-lives are longer than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphism may be more common among specific ethnic groups, such as African Americans and Hispanics. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving four or seven days of zidovudine plus lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10% - 12%. Use of nucleosides with a longer half-life such as tenofovir plus emtricitabine has also been shown to decrease nevirapine resistance after single dose treatment. The findings may however differ in patients on chronic nevirapine treatment. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from NNRTI to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of re-suppression of HIV RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the 2-NRTI. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than three weeks, some suggest that the PI-based regimen may need to be continued for up to four weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on etravirine and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping etravirine needs to be done

carefully using the same suggestions for nevirapine and efavirenz for the time being.

- **Discontinuation and reintroduction of nevirapine.** Because nevirapine is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a two-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than two weeks, nevirapine should be reintroduced with a dose escalation period of 200 mg once daily for 14 days, then a 200 mg twice-daily regimen **(AII)**.
- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B co-infection.** Patients with hepatitis B co-infection (hepatitis B surface antigen or HBeAg positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation. (See "Hepatitis B (HBV)/HIV Co-infection" section below.)

Considerations for Antiretroviral Use in Special Patient Populations

Acute HIV Infection

Panel's Recommendations

- Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time **(CIII)**.
- Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months **(CIII)**.
- If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels **(AIII)**.
- For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection **(AII)**.
- If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. If therapy is deferred, genotypic resistance testing should still be considered, because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.
- Since clinically significant resistance to PIs is less common than resistance to NNRTIs in treatment-naïve persons who harbor drug-resistant virus, consideration should be given to using a PI-based regimen if therapy is initiated before drug resistance test results are available **(BIII)**.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome and who report

recent high-risk behavior. However, in some settings, patients may not always disclose or admit to high risk behaviors, or might not perceive their behaviors as high-risk. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high risk behaviors.

When acute retroviral syndrome is suspected, a plasma HIV RNA test should be used in conjunction with an HIV antibody test to diagnose acute infection **(BII)**. Acute HIV infection is often defined by detectable HIV RNA in plasma in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test, since values in acute infection are generally very high (>100,000 copies/mL). A qualitative HIV RNA test can also be used in this setting. Patients diagnosed with acute HIV infection on the basis of either a quantitative or a qualitative HIV RNA test should have confirmatory serologic testing performed at a subsequent time point **(AI)** (see Table 11 in the original guideline document).

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in 6% to 16% of patients. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See "Drug Resistance Testing" section in the original guideline document.) If therapy is deferred, resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.

See Potential Benefits and Harms sections in this summary for information on potential benefits and risks of treating acute HIV infection.

HIV-Infected Adolescents

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for antiretroviral therapy are usually appropriate for postpubertal adolescents because HIV-infected adolescents who were infected sexually or through injecting-drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children.

Dosage for medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not solely on the basis of age. Adolescents in early puberty (i.e., Tanner Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in perinatally HIV-infected children, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than usual adult doses. Because data are not available to predict optimal medication doses for each antiretroviral 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 from pediatric to adult doses. Youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and who

are using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in selected circumstances to help guide therapy decisions under this context. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see the NGC summary: [Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection](#).

Adherence Concerns in Adolescents

HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health-care systems and who lack health insurance. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include:

- Denial and fear of their HIV infection
- Misinformation
- Distrust of the medical establishment
- Fear and lack of belief in the effectiveness of medications
- Low self-esteem
- Unstructured and chaotic lifestyles
- Lack of familial and social support
- Unavailable or inconsistent access to care or health insurance and incumbent risks of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used

For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents see the NGC summary: [Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection](#).

See the original guideline document for information on special considerations for adolescents and transitioning care.

HIV and Illicit Drug Users (IDUs)

See the original guideline document for information about the treatment challenges of HIV-infected IDUs and other illicit substance users, treatment efficacy in HIV-infected illicit drug use populations, and IDU/HIV drug toxicities and interactions.

It is usually possible over time to support most active drug users, such that acceptable adherence levels with antiretroviral agents can be achieved. Providers must work to combine all available resources to stabilize an active drug user to prepare them for antiretroviral therapy. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, and harm reduction strategies. A history of drug use alone is insufficient reason to withhold antiretroviral therapy, as those with a history of prior drug use have adherence rates similar to non-drug users.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and antiretroviral agents, including the increased risk for side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to antiretroviral agents that have a lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

HIV-Infected Women

Panel's Recommendations

- When initiating antiretroviral therapy for HIV-infected women, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents **(AI)**.
- Women taking antiretroviral agents that have drug interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy **(AIII)**.
- In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn **(AI)**.
- Genotypic resistance testing is recommended for all HIV-infected patients, including pregnant women, prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**.
- Selection of an antiretroviral combination in pregnant women should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy **(AIII)**.
- Efavirenz should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception **(AIII)**.
- Clinicians should consult the most current Public Health Service guidelines when designing a regimen for a pregnant patient **(AIII)**.

Women of Childbearing Potential

All women of childbearing potential should be offered preconception counseling and care as a component of routine primary medical care. Discussion should include special considerations with antiretroviral therapy use when trying to conceive and during pregnancy. (See the NGC summary: [Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#).) Antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception to prevent unintended pregnancy should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens, should pregnancy occur. These regimens should be avoided in women who are

trying to conceive or who are not using effective and consistent contraception. Counseling should be provided on an ongoing basis.

Pregnant Women

The decision to use any antiretroviral drug during pregnancy should be made by the woman after counseling and discussion with her clinician regarding the benefits versus risks to her, her fetus, and the newborn. Her decision should be respected; coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize personal, fetal, and neonatal well-being.

Prevention of Mother-to Child Transmission (PMTCT). Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT **(AI)**.

Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available, in which case therapy should be modified if the result demonstrates the presence of significant mutation(s) that may confer resistance to the prescribed antiretroviral regimen.

Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy, regardless of the infant's HIV status.

Regimen Considerations. Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of HIV-infected pregnant women are subject to unique considerations, which may result in different specific recommendations regarding timing of initiation and choice of drugs. These considerations include the following:

- Potential changes in pharmacokinetics, and thus dosing requirements, which result from physiologic changes associated with pregnancy
- Potential adverse effects of antiretroviral drugs in pregnant women
- Effect on the risk for perinatal HIV transmission
- Potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, all of which are unknown for many antiretroviral drugs

Clinicians should review the NGC summary: [Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#) for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care for therapy, both for the treatment of HIV infection and for PMTCT. Zidovudine by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks is recommended irrespective of antenatal regimen chosen.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (<http://www.apregistry.com/>). The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity.

Lastly, the women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for non-pregnant adults and adolescents.

Refer to the original guideline document for information on discontinuation of antiretroviral therapy postpartum.

Antiretroviral Considerations in Patients with Co-Infections

Hepatitis B (HBV)/HIV Coinfection

Treatment Recommendations for HBV/HIV Co-infected Patients

- All patients with HBV should be advised to abstain from alcohol; should receive hepatitis A vaccine, if found not to be immune at baseline (i.e., absence of hepatitis A total or IgG antibody); should be advised on methods to prevent HBV transmission (which do not differ from those to prevent HIV transmission); and should be evaluated for the severity of HBV infection.
- **If neither HIV nor HBV infection requires treatment:** Monitor the progression of both infections. If treatment becomes necessary for either infection, follow the guidelines listed in the scenarios below.
- **If treatment is needed for HIV but not for HBV:** The combination of tenofovir and emtricitabine or tenofovir and lamivudine should be used as the NRTI backbone of an antiretroviral regimen, which will result in treatment of both infections. To avoid development of HBV-resistant mutants, none of these agents should be used as the only agent with anti-HBV activity in an antiretroviral regimen.
- **If treatment for HBV is needed:** Patients who need treatment for HBV infection should also be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against both viruses: for example, tenofovir plus either emtricitabine or lamivudine. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk for resistance. If tenofovir cannot be used, another agent with anti-HBV activity should be used in combination with lamivudine or emtricitabine for treatment of HBV infection. Management of HIV should be continued with a combination regimen to provide maximal suppression.
- **Treating only HBV:** In instances when HIV treatment is not an option or is not desirable, pegylated interferon-alpha may be used for the treatment of HBV infection, as it does not lead to emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10 mg dose; however, there is a theoretical risk for development of HIV resistance, as it has anti-HIV activity at higher doses and is related to tenofovir. Because of the risk for HIV drug resistance, the use of emtricitabine, lamivudine, tenofovir, or entecavir without a full combination antiretroviral regimen should be avoided.

- **Need to discontinue emtricitabine, lamivudine, or tenofovir:** Monitor clinical course with frequent liver function tests, and consider the use of interferon, adefovir dipivoxil, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve.

Hepatitis C (HCV)/HIV Co-Infection

Assessment of HCV/HIV Co-Infection

Patients with HCV/HIV infection should be advised to avoid or limit alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A and B vaccine if found to be susceptible. All patients with HCV, including those with HIV co-infection, should be evaluated for HCV therapy.

Standard indications for HCV therapy in the absence of HIV infection are detectable plasma HCV RNA and a liver biopsy showing bridging or portal fibrosis. Alanine transaminase (ALT) levels may be elevated in association with HCV infection. However, ALT levels do not accurately reflect the severity of HIV-associated liver disease. Liver biopsy is important for HCV therapeutic decision making but is indicated only if the patient is considered a treatment candidate based on multiple other variables including severity and stability of HIV disease, other comorbidities, probability of adherence, and if there are contraindications to interferon-alpha, one of the drugs available for treatment of HCV.

Clinical trials in patients with HCV/HIV co-infection using pegylated interferon plus ribavirin for 48 weeks show sustained virologic response (SVR) rates of 60% to 70% for HCV genotype 2/3 but only 15% to 28% for genotype 1. These data are based on experience almost exclusively in carefully selected patients with CD4 counts >200 cells/mm³.

Treatment of HCV/HIV Co-Infection

Based on these observations, treatment of HCV is recommended according to standard guidelines with preference for those with higher CD4 counts (>200 cells/mm³). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible, but may be complicated by pill burden, drug toxicities, and drug interactions.

Scenarios for Treating HCV/HIV Co-Infection

Differences in HCV therapy management in the presence of HIV co-infection include:

- Ribavirin should not be given with didanosine because of the potential for drug-drug interactions leading to pancreatitis and lactic acidosis.
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is particularly important.
- Zidovudine combined with ribavirin is associated with higher rates of anemia suggesting this combination be avoided when possible.

- Growth factors to manage interferon-associated neutropenia and ribavirin-associated anemia may be required.

Mycobacterium Tuberculosis Disease or Latent Tuberculosis Infection with HIV Coinfection

Panel's Recommendations

- The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection **(AI)**.
- Presence of active tuberculosis requires immediate initiation of treatment **(AI)**.
- The optimal timing of initiation of antiretroviral therapy in patients with active TB disease is not known. In antiretroviral-naïve patients, delay of antiretroviral therapy for 2 to 8 weeks after initiation of TB treatment may allow for easier identification of causes of adverse drug reactions, and may reduce the risk of Immune Reconstitution Inflammatory Syndrome (IRIS or a "paradoxical reaction") once antiretroviral therapy is initiated. However, delay may increase the risk of HIV-related complications and mortality, particularly in those with very low CD4 cell counts **(BII)**.
- Directly observed therapy of TB treatment is strongly recommended for HIV-infected patients with active TB disease **(AII)**.
- Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving antiretroviral therapy, with dosage adjustment as necessary **(AII)**.
- Where available, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with antiretroviral therapy **(AII)**.
- Rifampin/rifabutin-based regimens should be given at least three times weekly in HIV-infected patients with active disease and CD4 count <100 cells/mm³; twice weekly is acceptable if CD4 count >100 cells/mm³ **(AII)**.
- Once-weekly rifapentine is not recommended in the treatment of active TB disease in HIV-infected patients **(AI)**.
- The optimal management of IRIS is unknown; TB treatment and antiretroviral therapy should be continued, along with use of non-steroidal anti-inflammatory agents for milder cases and consideration of the use of high dose corticosteroids for 1 to 4 weeks in severe cases, with the length of treatment and taper based on control of symptoms **(BIII)**.
- Immune restoration as a result of antiretroviral therapy may be associated with conversion from a negative to a positive tuberculin skin test (TST) or IFN-gamma release assay (IGRA) in response to *M. TB*-specific proteins; repeat TST or IGRA is recommended in previously TST-negative or IGRA-negative individuals after initiation of antiretroviral therapy when the CD4 cell count exceeds 200 cells/mm³ **(BII)**.
- HIV-infected individuals found to have latent TB infection (LTBI), defined as ≥ 5 mm skin test induration or positive IGRA with no prior treatment for LTBI and after appropriate evaluation to rule out active TB disease and no prior treatment of LTBI, should commence treatment with isoniazid (with pyridoxine) for 6 to 9 months **(AI)**.

Treatment of TB

Treatment of drug-susceptible TB disease in HIV-infected individuals should include the standard short-course regimen outlined in treatment guidelines, which consists of isoniazid (INH), rifampin (RIF) or rifabutin (RFB), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given for 2 months followed by INH + RIF for 4 to 7 months **(AI)**. Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. A minimum of thrice weekly treatment with rifamycin-containing TB treatment regimens is recommended for patients with a CD4 cell count <100 cells/mm³ **(AII)**. Once or twice weekly dosing has been associated with increased rates of development of rifamycin resistance in patients with advanced HIV, and once weekly rifapentine is not recommended **(AI)**.

Directly Observed Therapy (DOT)

DOT of TB treatment, in a manner supportive of the patients' needs is strongly recommended for patients with HIV/TB disease **(AII)**. In general, daily or thrice weekly DOT is recommended for the first two months and then three times weekly DOT for the continuation phase of 4 to 7 months **(BII)**.

Anti-TB/Antiretroviral Drug Toxicities and Interactions

Almost all antiretroviral drugs are associated with the potential for hepatotoxicity. INH, RIF, and PZA may also cause drug-induced hepatitis. These first line TB drugs should be used for treatment of active TB disease, if possible, even with coadministration of other potentially hepatotoxic drug or baseline liver disease **(AIII)**. Patients receiving drugs with potential hepatotoxicity should have frequent monitoring for clinical symptoms and signs of hepatitis and laboratory monitoring for hepatotoxicity, including serum aminotransferases, bilirubin, and alkaline phosphatase.

Limitations to Treatment Safety and Efficacy

Refer to the original guideline document for a discussion of the limits to treatment safety and efficacy, including adherence to antiretroviral therapy, adverse effects of antiretroviral agents, and drug interactions.

Prevention Counseling for the HIV-Infected Patient

Prevention counseling is an essential component of management for HIV-infected persons. Each patient encounter provides an opportunity to reinforce HIV prevention messages. Therefore, each encounter should include assessment and documentation of the following:

- Patient's knowledge and understanding of HIV transmission
- Patient's HIV transmission behaviors since the last encounter with a member of the health-care team

This should be followed by a discussion of strategies to prevent transmission that might be useful to the patient. Each member of the health care team can routinely

provide this counseling. Partner notification is a key component of HIV detection and prevention and should be pursued with the patient by the provider or by referral services.

Definitions:

Strength of the Evidence

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

Strength of Recommendation

- A. Strong recommendation for the statement
- B. Moderate recommendation for the statement
- C. Optional recommendation

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

Recommendations are based upon expert opinion and scientific evidence.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate use of antiretroviral agents in human immunodeficiency virus (HIV) infected adults and adolescents
- The primary goals of antiretroviral therapy are to improve and/or preserve immune function and reduce HIV-associated morbidity and mortality. A potential secondary benefit is the theoretical likelihood of reducing HIV transmission because of continued high-risk behaviors.

Potential Benefits of Early Antiretroviral Therapy

- Maintenance of a higher CD4 count and prevention of potentially irreversible damage to the immune system
- Decreased risk for HIV-associated complications that can sometimes occur at CD4 counts >350 cells/mm³, including tuberculosis, non-Hodgkin's

- lymphoma, Kaposi's sarcoma, peripheral neuropathy, human papillomavirus (HPV)-associated malignancies, and HIV-associated cognitive impairment
- Decreased risk of nonopportunistic conditions, including cardiovascular disease, renal disease, liver disease, and non acquired immune deficiency syndrome (AIDS)-associated malignancies and infections
 - Decreased risk of HIV transmission to others, which will have positive public health implications

Potential Benefits of Treating Acute Infection

Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression. Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission. Additionally, although data are limited and the clinical relevance is unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by the early initiation of antiretroviral therapy.

POTENTIAL HARMS

Potential Risks of Early Antiretroviral Therapy

- Development of treatment-related side effects and toxicities
- Development of drug resistance because of incomplete viral suppression, resulting in loss of future treatment options
- Less time for the patient to learn about human immunodeficiency virus (HIV) and its treatment and less time to prepare for the need for adherence to therapy
- Increased total time on medication, with greater chance of treatment fatigue
- Premature use of therapy before the development of more effective, less toxic, and/or better studied combinations of antiretroviral drugs
- Transmission of drug-resistant virus in patients who do not maintain full virologic suppression

Potential Risks of Treating Acute HIV Infection

The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy, and adverse effect on quality of life.

Refer to the original guideline document, including Tables 7, 9, 13, and 14, for important and more detailed information regarding the adverse effects associated with antiretroviral drugs, highly active antiretroviral therapy, and potential drug interactions.

CONTRAINDICATIONS

CONTRAINDICATIONS

See Tables 14 through 16 in the original guideline document for drug combinations that should be avoided.

Some antiretroviral regimens or components are not recommended for human immunodeficiency virus type 1 (HIV-1) infected patients due to suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. See "What Not to Use" in the "Major Recommendations" field for detailed information.

- *Efavirenz* is contraindicated in the first trimester of pregnancy; avoid use in women with pregnancy potential.
- *Nevirapine* is contraindicated in patients with moderate or severe (Child Pugh B or C) hepatic impairment.
- *Protease inhibitors (PIs)* are contraindicated with proton pump inhibitors.
- *Atazanavir (unboosted)* is contraindicated with proton pump inhibitors.
- *Tipranavir/ritonavir* is contraindicated in patients with moderate to severe (Child-Pugh class B & C) hepatic insufficiency.
- *Stavudine and zidovudine* coadministration is contraindicated because of virologic antagonism.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines, therefore, are updated frequently by the Panel and are available as a "living document" at the <http://www.aidsinfo.nih.gov> Web site. However, these guidelines cannot always keep pace with the rapid evolution of new data in this field, and the guidelines cannot provide guidance for all patients. Therefore, clinicians need to exercise good judgment in management decisions tailored to unique patient circumstances.
- The Panel has carefully reviewed recent results from clinical trials in human immunodeficiency virus (HIV) therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the panel attempted to reflect reasonable options in its conclusions.
- HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context is well known. Guidelines are only a starting point for medical decision-making. They can identify some of the boundaries of high care quality, but cannot substitute for sound judgment.
- Information included in these guidelines may not represent U.S. Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with FDA-defined legal standards for product approval.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2008 Nov 3. 139 p. [558 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Dec 1 (updated 2008 Nov 3)

GUIDELINE DEVELOPER(S)

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Department of Health and Human Services (U.S.) - Federal Government Agency [U.S.]

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Office of AIDS Research, National Institutes of Health

GUIDELINE COMMITTEE

Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a Working Group of the Office of AIDS Research and Advisory Council)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Panel submit a written financial disclosure annually. The current list as of February 2008 is available in Appendix A in the original guideline document. An updated list will be available at the [AIDSinfo Web site](#) after February 2009.

GUIDELINE STATUS

This is the current release of the guideline. It was last updated on November 3, 2008.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines, therefore, are updated frequently by the Panel and are available as a "living document" at the <http://www.aidsinfo.nih.gov> Web site.

Status information regarding this guideline is available from the [AIDSinfo Web site](#), telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

GUIDELINE AVAILABILITY

Electronic copies of the guideline: Available in Portable Document Format (PDF) from the [AIDSinfo Web site](#).

The guideline is also available for Palm OS or Pocket PC download from the [AIDSinfo Web site](#).

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: www.cdcnpin.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Clinical management of the HIV-infected adult. A manual for midlevel clinicians. 1993 Sep (revised 2006). 399 p. Electronic copies: Available in Portable Document Format (PDF) from the [AIDSinfo Web site](#).

Print copies: Available from Southeast AIDS Training and Education Center, Emory University School of Medicine, 735 Gatewood Road, NE, Atlanta, GA 30322. Telephone: (404) 727-2929; fax (404) 727-4562. E-mail: seatec@emory.edu. Web site: www.seatec.emory.edu.

The following Power Point slide sets based on the "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents" are also available:

- Comprehensive guideline summary. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Nov . 53 slides. Available from the [AETC Web site](#).
- Initiation of therapy. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Nov. 73 slides. Available from the [AETC Web site](#).
- Managing the treatment-experienced patient. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Nov. 37 slides. Available from the [AETC Web site](#).
- Special issues. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Nov. 57 slides. Available from the [AETC Web site](#).

The following are also available:

- Antiretroviral Pocket Reference Cards. Antiretroviral therapy in adults and adolescents. AIDS Educational and Training Center (AETC) 2008 Mar. Available from the [AETC Web site](#).
- A comprehensive Spanish-language Web site featuring information about HIV treatment and clinical trials is available at <http://aidsinfo.nih.gov/infoSIDA/>.

PATIENT RESOURCES

The following are available:

- HIV and its treatment: what you should know. Bethesda (MD): Department of Health and Human Services (DHHS); 2008 Feb. 15 p. Electronic copies: Available in Portable Document Format (PDF) from the [AIDSinfo Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).
- Side effects of anti-HIV medications. Health information for patients. Bethesda (MD): Department of Health and Human Services (DHHS); 2005 Oct. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the [AIDSinfo Web site](#). See the related QualityTool summary on the [Health Care Innovations Exchange Web site](#).

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012, International number (301)-562-1098. Web site: <http://www.cdcnpin.org>.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the

authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on July 20, 1999. The original information was verified by the guideline developer on August 10, 1999. Updated guidelines were issued on January 28, 2000, February 5, 2001, April 23, 2001, August 17, 2001, February 4, 2002, July 14, 2003, November 10, 2003, November 17, 2003, and March 29, 2004. This summary was updated on November 1, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was updated on April 12, 2005. An addendum was included on July 18, 2005. This NGC summary was updated on October 10, 2005 and May 10, 2006. This summary was updated by ECRI on July 3, 2006, following the U.S. Food and Drug Administration advisory on Aptivus (tipranavir). This summary was updated on October 12, 2006. This summary was updated by ECRI on April 16, 2007, following the U.S. Food and Drug Administration advisory on Baraclude (entecavir). This summary was updated most recently by ECRI Institute on May 2, 2007. This summary was updated by ECRI Institute on September 5, 2007, following the revised U.S. Food and Drug Administration advisory on Baraclude (entecavir). This summary was updated by ECRI Institute on October 2, 2007, following the U.S. Food and Drug Administration advisory on Viracept (nelfinavir mesylate). This NGC summary was updated by ECRI Institute on December 4, 2007. This NGC summary was updated by ECRI Institute on February 7, 2008. This summary was updated by ECRI Institute on March 28, 2008, following the FDA advisory on Prezista (darunavir). This summary was updated by ECRI Institute on August 11, 2008 following the U.S. Food and Drug Administration advisory on Ziagen (abacavir sulfate). This summary was updated by ECRI Institute on November 21, 2008.

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