Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations of the International AIDS SocietyUSA Panel

Melanie A. Thompson; Judith A. Aberg; Pedro Cahn; et al.

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Antiretroviral Treatment of Adult HIV Infection
2010 Recommendations of the International AIDS Society–USA Panel

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SUCCESSFUL ANTIRETROVIRAL therapy (ART) is associated with dramatic decreases in AIDS-defining conditions and their associated mortality. Expansion of treatment options and evolving knowledge require revision of guidelines for the initiation and long-term management of ART in adults with HIV infection.

Since the 2008 International AIDS Society–USA ART guidelines,1 new data have emerged regarding timing of therapy, optimal regimen choices, and monitoring. There are also issues of special relevance to circumstances such as pregnancy, hepatitis virus coinfections, kidney disease, cardiovascular disease, and primary HIV infection.

Analyses of clinical trials and epidemiologic cohorts have shed light on the role of ART in mitigating serious non-AIDS events associated with uncontrolled HIV replication. Newer drugs are better understood in terms of efficacy, toxicity, and potential uses. New data also suggest a role for ART in the prevention of HIV transmission.

METHODS
The panel was convened in 1995 to develop evidence-based recommendations for ART for HIV-infected adults in developed-world settings.2 Members are appointed by International AIDS Society–USA according to clinical and research expertise. Current panel members do not participate in pharmaceutical marketing or promotional activities (eg, speakers’ bureaus, industry satellites) during tenure on the panel. The current panel convened in January 2010 and met weekly in person or by teleconference.

Context Recent data regarding the consequences of untreated human immunodeficiency virus (HIV) infection and the expansion of treatment choices for antiretroviral-naive and antiretroviral-experienced patients warrant an update of the International AIDS Society–USA guidelines for the use of antiretroviral therapy in adults with HIV infection.

Objectives To provide updated recommendations for management of HIV-infected adults, using antiretroviral drugs and laboratory monitoring tools available in the international, developed-world setting. This report provides guidelines for when to initiate antiretroviral therapy, selection of appropriate initial regimens, patient monitoring, when to change therapy, and what regimens to use when changing.

Data Sources and Study Selection A panel with expertise in HIV research and clinical care reviewed relevant data published or presented at selected scientific conferences since the last panel report through April 2010. Data were identified through a PubMed search, review of scientific conference abstracts, and requests to antiretroviral drug manufacturers for updated clinical trials and adverse event data.

Data Extraction and Synthesis New evidence was reviewed by the panel. Recommendations were drafted by section writing committees and reviewed and edited by the entire panel. The quality and strength of the evidence were rated and recommendations were made by full panel consensus.

Conclusions Patient readiness for treatment should be confirmed before initiation of antiretroviral treatment. Therapy is recommended for asymptomatic patients with a CD4 cell count ≥500/µL, for all symptomatic patients, and those with specific conditions and comorbidities. Therapy should be considered for asymptomatic patients with CD4 cell count >500/µL. Components of the initial and subsequent regimens must be individualized, particularly in the context of concurrent conditions. Patients receiving antiretroviral treatment should be monitored regularly; treatment failure should be detected and managed early, with the goal of therapy, even in heavily pretreated patients, being HIV-1 RNA suppression below commercially available assay quantification limits.

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were considered (eFigure, available at http://www.jama.com). Data on file and personal communications were not considered except for data and safety monitoring board reports and US Food and Drug Administration alerts.

For identification of evidence, one member (P.A.V.) conducted a PubMed search of reports published since the last update. Search terms were HIV and antiretroviral, limited to humans, clinical trials, meta-analyses, randomized controlled trials, reviews, English, and adult, and yielded 582 citations. Of those, 194 citations were selected for review, eliminating those not relevant to adult care in resource-rich settings. Section teams identified abstracts from scientific conferences. Drug manufacturers were asked to provide published or presented data on updated clinical trials and adverse events for their products.

Section team leaders (J.A.A., P.C., J.S.G.M., G.R., and A.T.) summarized section consensus for group review and discussion. The quality and strength of evidence were rated for each recommendation (eBox). Final recommendations were by full panel consensus.

WHEN TO START
Established HIV-1 Infection

Deciding to start ART requires weighing the benefits of treatment on morbidity and mortality against its risks, including toxicity, resistance, drug interactions, and the costs and inconvenience of lifelong treatment. Sustained viral suppression restores and preserves immunologic function, decreasing opportunistic diseases and mortality. The patient must be ready and willing to adhere to lifelong therapy. Advances in ART continue to shift the therapeutic risk-benefit balance to earlier treatment. Improvements in potency, toxicity and tolerability, and pill burden allow for durable viral suppression for most patients.

The risks associated with ART have decreased, whereas concerns regarding the risks of long-standing untreated viremia have increased. Uncontrolled HIV replication and immune activation lead to a chronic inflammatory state, resulting in end-organ damage and comorbid conditions not previously thought to be associated with HIV infection. Several studies have shown that the life span of those with HIV infection still falls short of that of the general population, even at higher CD4 cell counts.6,3-6 This life span decrease is related to serious, non-AIDS events attributed to chronic immune activation and the potentially permanent immune damage associated with prolonged immune depletion. In several data sets,3-8 non-AIDS events were associated with elevated levels of viral replication and markers of immune activation and coagulation (including D-dimer, interleukin 6, or high-sensitivity C-reactive protein). Mortality from non-AIDS events now exceeds that of AIDS-defining opportunistic diseases in individuals receiving effective ART.9-11

The strength of evidence supporting initiation of therapy increases as CD4 cell count decreases. In a cohort of 17 517 asymptomatic HIV-infected persons, initiating ART at a CD4 cell count greater than 500/µL decreased mortality by 94%, and initiating it at a CD4 cell count between 351 and 500/µL decreased mortality by 69%, although the numbers of deaths were low in both groups. The majority of deaths were from non-AIDS conditions.10 In an analysis of 62 760 persons in 12 cohorts, reduction in death was 23% and 45% for those beginning therapy with a CD4 cell count greater than 500/µL and 350 to 500/µL, respectively.13

Data from prospective observational cohorts and clinical trials demonstrate worse outcomes among patients who begin receiving ART at CD4 cell counts less than 350/µL or who have symptomatic HIV disease.1 Among 24 444 patients from 18 cohorts, there was no additional benefit from initiating therapy at CD4 cell counts of 451 to 550/µL compared with 351 to 450/µL. However, this analysis included only persons who began receiving ART at less than 550/µL.13 A randomized trial addressing the timing of initiation of therapy is under way. Indicators of rapid progression of disease, such as high HIV-1 RNA and rapid CD4 cell count decline, are recognized as reasons to initiate ART regardless of CD4 cell count.1 Older age is also associated with higher risk of AIDS and non-AIDS-related deaths. Pregnant women should be treated at least by the second trimester and therapy continued after birth.5,10,14-18

Special Considerations

HIV increases the risk of liver-related mortality in those with hepatitis B virus (HBV).19 Hepatitis B infection should not be treated with lamivudine or emtricitabine alone. If tenofovir is contraindicated, entecavir should be added.20 The durability of entecavir is compromised by previous HBV treatment failure with regimens including emtricitabine or lamivudine.21 Flares of hepatocellular inflammation may occur when therapy with agents active against HBV is discontinued or when HBV resistance to lamivudine or emtricitabine emerges in patients receiving these agents without tenofovir or entecavir.21,22 If ART must be interrupted, patients should be closely monitored for HBV reactivation.21

Patients with HIV–hepatitis C virus (HCV) coinfection progress to end-stage liver disease more rapidly than do HCV monoinfected patients.23 Clearance of HCV is associated with regression of liver fibrosis and a reduced risk of ART-related hepatotoxicity.24 In one study, abacavir with ribavirin was associated with a reduced rate of sustained HCV virologic response.25 Zidovudine, didanosine, and stavudine have overlapping hematologic and hepatic toxicities with current HCV therapy.23 Patients with HCV coinfection are at increased risk of hepatotoxicity, and certain ART regimens may require dose adjustment (see “Monitoring” section). Current HCV therapy has a higher probability of sustained HCV virologic response with HCV genotype 2 or 3; therefore, for patients with a high CD4 cell count and no imperative to begin ART, HCV treatment before ART may avoid cumulative drug toxicity and drug interactions.20

Renal disease ranges from HIV-associated nephropathy, to HIV-associated immune complex kidney disease, to...
verse risk of developing chronic kidney disease. Dependently associated with an increase in mortality by 56% compared with initiating ART after completion of TB treatment. Immune reconstitution inflammatory syndromes occurred more often with early therapy, but no changes in ART were needed and no deaths were related to immune reconstitution inflammatory syndromes. Consideration must be given to the potential for drug interactions among therapies for opportunistic infections and ART.

Patients who present with symptomatic primary HIV infection may progress more rapidly than those who present without symptoms. Antiretroviral therapy reduces the extremely high viral loads in primary infection and may reduce transmission. For patients presenting with asymptomatic primary infection, there are insufficient data for a recommendation on whether to treat immediately or defer; however, an analysis of 3019 seroconverters showed a 78% reduction in mortality when ART was initiated rather than delayed.

Antiretroviral therapy reduces HIV transmission. Widespread use of ART during pregnancy has nearly eliminated mother-to-child transmission in the developed world. A meta-analysis concluded that ART also decreases the risk of HIV transmission to uninfected partners in HIV-serodiscordant heterosexual couples, and a cohort study of 3381 heterosexual serodiscordant couples showed a 92% reduction in transmission when ART was used by the infected partner. Another cohort study showed a strong association between increased ART coverage, decreased community plasma viral load, and decreased HIV incidence among injection drug users. Some mathematic models suggest that more aggressive ART coverage could reduce the incidence of new HIV infections; some field data also support this.

**Recommendations**

Patient readiness for treatment is a key consideration when deciding when to initiate ART. There is no CD4 cell count threshold at which initiating therapy is contraindicated. Initiation of therapy is recommended (Table 1) for symptomatic patients with established disease, regardless of CD4 cell count (AIIa), and for asymptomatic individuals with CD4 cell counts less than or equal to 500/µL (AIIa for < 350/µL, AIIa for ≤ 500/µL). Treatment should be considered for asymptomatic individuals with CD4 cell counts greater than 500/µL (CII). Therapy is recommended regardless of CD4 cell count in the following settings: increased risk of disease progression associated with a rapid decline in CD4 cell count (ie, > 100/µL per year) or a plasma HIV-1 RNA level greater than 100,000 copies/mL (AIIa); older than 60 years (BIIa); pregnancy (at least by the second trimester) (AIIa); or chronic HBV or HCV coinfection (BIIa), although for patients with HCV genotype 2 or 3 and high CD4 cell counts, an attempt to eradicate HCV may be undertaken before ART is initiated (BIIa); HIV-associated kidney disease (BIIa), avoiding drugs with potential adverse effects on the kidney (tenofovir, indinavir, atazanavir), if possible (AIIa); high cardiovascular risk (BIIa), modifiable risk factors for cardiovascular disease should be aggressively managed (AIIa); opportunistic infections, including tuberculosis, with attention to drug interactions and the potential for immune reconstitution inflammatory syndromes (AIIa); and symptomatic primary HIV infection to prevent rapid progression, to preserve immune function, and to limit ongoing transmission from this high-risk population (BIIa). Once initiated, ART should be continued, except in the context of a clinical trial (AIIa). Therapy should be considered where there is a heightened risk of HIV transmission (ie, HIV-serodiscordant couples) (BIIa), without supplanting traditional prevention approaches. Risk reduction counseling should be a routine part of care at each patient-clinician interaction.

**WHAT TO START**

Selecting an initial regimen has long-standing consequences for future therapy. The initial regimen should be individualized according to resistance testing results and predicted virologic efficacy, tox-
Table 1. Recommendations for Initiating Antiretroviral Therapy (ART) in Treatment-Naive Adults With HIV-1 Infection Who Are Ready to Begin Therapy \(^a\)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Recommendation</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic HIV disease</td>
<td>ART is recommended regardless of CD4 cell count</td>
<td>Alfa</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/mL</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>Rapid decline in CD4 cell count, &gt;100/µL per year</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>Active hepatitis B or C virus coinfection</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>Active or high risk for cardiovascular disease</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>Symptomatic primary HIV infection</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>Risk for secondary HIV transmission is high, eg, serodiscordant couples</td>
<td>ART</td>
<td>Alfa</td>
</tr>
<tr>
<td>Asymptomatic, CD4 cell count ≤500/µL</td>
<td>ART is recommended</td>
<td>Alfa</td>
</tr>
<tr>
<td>CD4 cell count &lt;350/µL</td>
<td>ART should be considered, unless patient is an elite controller (HIV-1 RNA &lt;50 copies/mL) or has stable CD4 cell count and low-level viremia in the absence of ART</td>
<td>CII</td>
</tr>
<tr>
<td>CD4 cell count 350-500/µL</td>
<td>ART should be considered, unless patient is an elite controller (HIV-1 RNA &lt;50 copies/mL) or has stable CD4 cell count and low-level viremia in the absence of ART</td>
<td>CII</td>
</tr>
</tbody>
</table>

Abbreviation: HIV, human immunodeficiency virus.

\(^a\)Details, cautions, considerations, and supporting data are described in the text. Ratings are described in the eBox (http://www.jama.com).

Tenofovir has activity against both HIV-1 and HBV and a long intracellular half-life. Potent viral suppression and CD4 cell count increases occur when tenofovir and emtricitabine are used with a third agent. Alternative nRTIs are preferred over dose-adjusted tenofovir for patients with renal dysfunction. \(^55\) Tenofovir concentrations can be increased by some protease inhibitors (PIs), and studies have suggested a greater risk of renal dysfunction when tenofovir is used in PI-based regimens. \(^56\) Tenofovir is available in fixed-dose, once-daily formulations with emtricitabine and with emtricitabine plus efavirenz.

HLA-B*5701 testing identifies persons at high risk for abacavir hypersensitivity. \(^39,60\) In the AIDS Clinical Trials Group study A5202, inferior virologic responses were observed with abacavir plus lamivudine compared with tenofovir plus emtricitabine in subjects with baseline HIV-RNA levels greater than 100,000 copies/mL. \(^56,61\) Abacavir plus lamivudine was also associated with more lipid abnormalities. \(^51,62\) The Data Collection on Adverse Events of Anti-HIV Drugs study, a large multinational observational cohort, found that recent, current, or cumulative use of abacavir predicted an increased risk of myocardial infarction, an association not observed with tenofovir. \(^53,64\) This risk was accentuated in participants who had pre-existing cardiovascular risk factors. In contrast, in a pooled analysis of 52 clinical trials involving more than 9500 participants who received abacavir, no increased risk of myocardial infarction was found. \(^65\) Thus, no consensus has yet been reached on either the association or a possible mechanism. \(^66\)

Lamivudine and emtricitabine are each well tolerated and select for the M184V mutation, which confers high-level resistance to both drugs but enhances the activity of tenofovir. Both are active against HBV but should only be used in combination with a second HBV-active drug when treating HIV-HBV coinfected patients. The role of zidovudine in initial regimens is limited by tolerability issues, as well as increased risk for lipodystrophy and hyperlipidemia compared with tenofovir. \(^1\) Stavudine and didanosine are not recommended for initial therapy because of increased toxicity of each. \(^1\) Combination regimens including 3 or 4 nRTIs alone are not recommended because of suboptimal virologic activity and increased toxicity. \(^1,67\)

Nonnucleoside Reverse Transcriptase Inhibitors

Several studies have shown consistently high and sustained rates of viral suppression with efavirenz in the initial regimen. \(^1,68\) Efavirenz was virologically superior to ritonavir-boosted lopinavir (lopinavir/r) \(^69,70\) and comparable to atazanavir/r \(^65,62,71\) and raltegravir. \(^71\) In AIDS Clinical Trials Group A5142 and 2 other studies, lopinavir/r showed better CD4 cell count responses and less drug resistance after virologic failure than efavirenz. \(^69,72,73\) Efavirenz is associated with rash and central nervous system adverse effects and should not be used during the first trimester of pregnancy or in women of childbearing age trying to conceive or not using effective and consistent contraception. \(^75\) Efavirenz is an inducer of cytochrome P450, and potential drug interactions are an important consideration. Baseline genotypic testing is important when considering nonnucleoside reverse transcriptase inhibitor (NNRTI) use. Primary NNRTI resistance rates vary from approximately 8.1% in the United States to 2.3% in Europe. \(^74,76\)

Nevirapine was noninferior to atazanavir/r (each combined with tenofovir plus emtricitabine) in a randomized controlled trial restricted to women and men.
with CD4 cell counts less than 250/µL and 400/µL, respectively.\textsuperscript{77} Nevirapine was similar virologically to lopinavir/r (again, each with tenofovir/emtricitabine) in a randomized trial of 500 African women with CD4 cell counts less than 200/µL.\textsuperscript{78} However, drug discontinuation because of adverse events was higher among nevirapine recipients.\textsuperscript{79,80} Serious hepatic events have been described within the first several weeks of initiation of nevirapine-based therapy but are less frequent if nevirapine is restricted to pretreatment CD4 cell counts less than 250/µL (women) or less than 400/µL, respectively.\textsuperscript{77}

### Box. Recommended Components of the Initial Antiretroviral Regimen\textsuperscript{a}

**Dual nRTI Component**

- **Recommended**
  - Tenofovir/emtricitabine
    - Available as fixed-dose combination alone and with efavirenz
    - Once daily
    - Low genetic barrier to resistance (emtricitabine)
    - Renal dysfunction, decreased bone mineral density associated with tenofovir influence choice

- **Alternative**
  - Abacavir/lamivudine
    - Available as fixed-dose combination
    - Once daily
    - Weaker antiviral efficacy in treatment-naive patients with baseline HIV-1 RNA >100,000 copies/mL than tenofovir/emtricitabine
    - Low genetic barrier (lamivudine)
    - Need to screen for HLA-B*5701\textsuperscript{b} to reduce risk of abacavir hypersensitivity
    - Abacavir may be associated with increased cardiovascular risk

**Key Third Agent**

- **Recommended**
  - Efavirenz\textsuperscript{b}
    - NNRTI class
    - Available in fixed-dose combination with tenofovir/emtricitabine, which has become standard-of-care comparator regimen in most clinical trials
    - Low genetic barrier
    - Major psychiatric illness, first trimester of pregnancy, or intention to become pregnant influences choice

- **Alternatives**
  - Atazanavir/r\textsuperscript{b}
    - PI/r class
    - Once daily
    - Widely prescribed when PI/r is chosen for initial therapy
    - Leaves options for future regimens
    - Less lipidogenic potential than lopinavir/r
    - Hyperbilirubinemia, need for acid-reducing agents, and risk of nephrolithiasis influence choice
  - Darunavir/r\textsuperscript{c}
    - PI/r class
    - Once daily in treatment-naive patients
    - Limited experience in treatment-naive patients, presence of other options in most naive patients, and efficacy in patients with treatment experience, and multidrug-resistant virus influence choice
    - Raltegravir\textsuperscript{c}
      - INSTI class (only 1 FDA approved at present time)
      - Twice daily
      - Low drug interaction potential
      - Rapid decline in HIV-1 RNA slope after initiation
      - Low genetic barrier
      - Limited experience in naive patients, presence of other options in most naive patients, and efficacy in treatment-experienced patients with multidrug-resistant virus influence choice

**Alternatives**

- **Lopinavir/r**
  - PI/r class
  - Extensive clinical experience
  - Comparator PI/r in many trials
  - Only PI coformulated with ritonavir (heat stable)
  - Can be given once daily in naive patients
  - Potential for hyperlipidemia and gastrointestinal adverse effects influences choice

- **Fosamprenavir/r**
  - PI/r class
  - Profile similar to lopinavir/r
  - May be useful when other initial PI/r not tolerated

- **Maraviroc**
  - CCR5 antagonist class
  - Targets host protein (viral coreceptor)
  - Need to perform viral tropism assay before use
  - Limited clinical experience in treatment-naive patients
  - Strategically, may be more useful in treatment-experienced patients or when primary (transmitted) drug resistance is present but viral population should be exclusively receptor 5

Abbreviations: CCR5, CC chemokine receptor 5; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside or nucleotide analogue reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir boosted.

\textsuperscript{a} Details, cautions, considerations, and supporting data\textsuperscript{1,17,55-105} are described in the text.

\textsuperscript{b} Based on extensive clinical experience.

\textsuperscript{c} Based on antiviral efficacy and tolerability comparable to that of key third agents but more limited experience in treatment-naive patients.
400/μL (men). Patients who experienced CD4 cell count increases to levels above these thresholds with undetectable viremia as a result of previous ART safely switched to nevirapine therapy. The efficacy in initial therapy of etravirine, a newer NNRTI, has not yet been reported.

Protease Inhibitors
Atazanavir/r has greater virologic activity than unboosted atazanavir when combined with 2 nRTIs. Once-daily atazanavir/r and twice-daily lopinavir/r, both combined with tenofovir plus emtricitabine, showed similar virologic and CD4 cell count responses at 48 and 96 weeks. The hyperbilirubinemia, scleral icterus, or frank jaundice associated with atazanavir exposure is not accompanied by hepatic transaminase elevations but is more frequent with ritonavir boosting. Nephrolithiasis has occurred uncommonly with atazanavir, with or without ritonavir, and the eGFR may decrease when atazanavir is combined with tenofovir. Unboosted atazanavir should not be used with tenofovir. Atazanavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that increase gastric pH, such as antacids, H2 antagonists, and particularly proton-pump inhibitors, may impair absorption of atazanavir and compromise its activity.

Darunavir/r once daily was compared with standard doses of lopinavir/r (once or twice daily), each in combination with tenofovir plus emtricitabine. At 48 weeks, darunavir/r was noninferior to lopinavir/r, but virologic response rates were lower in the lopinavir/r arm among subjects with baseline HIV-1 RNA levels greater than 100,000 copies/mL. At 96 weeks, darunavir/r was virologically superior to lopinavir/r, but virologic response rates were lower in the lopinavir/r arm among subjects with baseline HIV-1 RNA levels greater than 100,000 copies/mL. At 96 weeks, darunavir/r was virologically superior to lopinavir/r, but virologic response rates were lower in the lopinavir/r arm among subjects with baseline HIV-1 RNA levels greater than 100,000 copies/mL.

Entry Inhibitors
The CC chemokine receptor 5 (CCR5) inhibitor maraviroc was compared with efavirenz, both in combination with zidovudine plus lamivudine, in 633 subjects with CCR5-tropic virus and no evidence of resistance to the study drugs. At 48 weeks, HIV-1 RNA less than 50 copies/mL was achieved in 65% and 69% of maraviroc and efavirenz recipients, respectively. The results did not meet prespecified criteria for noninferiority for maraviroc. Through 48 weeks, more participants discontinued maraviroc because of lack of efficacy (11.9% and 4.2%, respectively), whereas fewer participants discontinued maraviroc because of toxicity (4.2% and 13.6%, respectively). Follow-up results at 96 weeks demonstrated durable responses in both groups. Reanalysis of the results with a more sensitive tropism assay or with a genotype-based approach suggested that the differences between treatment arms could be attributed to misclassification of tropism in some patients by the older assay.

If only subjects with R5 virus at entry were considered, maraviroc appeared similar to efavirenz in antiretroviral activity. Maraviroc has not been evaluated extensively with other nRTI backbones in initial therapy.

Recommendations
Fixed-dose combinations are recommended when possible for convenience. Tenofovir plus emtricitabine is the recommended nRTI combination in initial therapy (A1a). If tenofovir plus emtricitabine cannot be used, abacavir plus lamivudine may be used as an alternative when HLA B*5701 testing results are negative, keeping in mind abacavir’s lower efficacy at high viral loads (A1a) and its possible association with increased cardiovascular risk (AIIa). Zidovudine plus lamivudine should be reserved for instances in which neither tenofovir nor abacavir can be used. Three or 4 nRTIs alone are not recommended for initial therapy (A1a). Efavirenz (A1a), atazanavir/r (A1a), darunavir/r (A1a), or raltegravir (A1a) is recommended as the third component of an initial regimen. More evidence is available for efavirenz and atazanavir/r than...
for darunavir/r or raltegravir. Lopinavir/r, fosamprenavir/r, and maraviroc are alternative third-component choices (Ala). Neither saquinavir/r nor unboosted PIs, including atazanavir, are recommended for initial therapy (Bla). Nevirapine should be used as an alternative initial therapy only with pretreatment CD4 cell counts less than 250/µL (women) or less than 400/µL (men) (BII). Considerations for initial therapy in patients with specific conditions are summarized in Table 2.

**MONITORING**

Effective therapy should result in suppression to less than 50 copies/mL (polymerase chain reaction) or 75 copies/µL (branched DNA) by 24 weeks, regardless of previous treatment experience. Frequent HIV-1 RNA monitoring is recommended during the first year of ART to detect failure. Testing of HIV-1 RNA should be repeated 2 to 8 weeks after initiation, every 4 to 8 weeks until suppressed, and then every 3 to 4 months for at least the first year. CD4 cell counts should be monitored at least every 3 to 4 months after initiation of therapy, especially among patients with counts less than 200/µL, to determine the need for continuing opportunistic infection prophylaxis. In a EuroSIDA study, patients who maintained stable and fully suppressive ART for 1 year had a low chance of experiencing treatment failure in the ensuing months. Therefore, once viral replication is suppressed, monitoring intervals may be extended up to every 6 months among patients who remain virologically suppressed and have CD4 cell counts greater than 350/µL. More frequent monitoring is required for patients who have changed therapy because of virologic failure.

Changes in assay methodology may result in detectable viral load in individuals with previously undetectable viremia. Detection artifacts have also been attributed to specific plasma processing practices. New assays may soon be available with a lower limit of 20 copies/µL; however, the clinical implications of viremia between 20 and 50 copies/µL are not yet clear. Confirmed viral load rebound on 2 separate tests at least 2 to 4 weeks apart should prompt a careful evaluation of regimen tolerability, drug-drug interactions, and patient adherence.

The prevalence of transmitted drug resistance varies in resource-rich societies from 8% to 16%. Baseline genotyping is recommended for patients with viral loads greater than 100,000 copies/mL of HIV RNA at baseline (see text).

**Table 2. Initial Antiretroviral Therapy (ART) and Considerations in Patients With Specific Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Possible Backbone Drugs</th>
<th>Third Agent</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High atherosclerotic cardiovascular risk</td>
<td>Emtricitabine, lamivudine, tenofovir</td>
<td>Efavirenz, nevirapine, atazanavir/r, raltegravir</td>
<td>Initiation of ART, regardless of CD4 cell count, is recommended. If possible avoid abacavir, fosamprenavir/r, indinavir/r, lopinavir/r because of an associated increased risk of cardiovascular events.</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Emtricitabine, lamivudine, tenofovir. Use 2 HBV-active drugs. Do not use abacavir or abacavir/ lamivudine alone for treatment of HBV in coinfected patients.</td>
<td>Efavirenz, raltegravir, nevirapine, maraviroc, PI/r</td>
<td>Initiate ART regardless of CD4 cell count (BIIa). Monitor alanine aminotransferase after ART initiation and after withdrawal of suppressive therapy.</td>
</tr>
<tr>
<td>Chronic HBV infection requiring therapy</td>
<td>Emtricitabine, lamivudine, tenofovir.</td>
<td>Efavirenz, raltegravir, PI/r should be monitored for hepatotoxicity. Avoid nevirapine except for women with CD4 (&lt;250/µL) and men with (&lt;400/µL). Maraviroc should be used with caution in patients with liver disease.</td>
<td>ART that includes tenofovir/emtricitabine should be used irrespective of CD4 cell count (BIIa).</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Complete recommendations for the use of antiretroviral therapy in pregnant women are available at <a href="http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf">http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf</a> and <a href="http://www.europeanadstclinicalsociety.org">http://www.europeanadstclinicalsociety.org</a></td>
<td>PI/r should be monitored for hepatotoxicity. Avoid nevirapine except for women with CD4 (&lt;250/µL) and men with (&lt;400/µL). Maraviroc should be used with caution in patients with liver disease.</td>
<td>ART should generally be initiated first in all patients with HCV coinfection regardless of CD4 cell count to slow liver disease progression (BIIa), except possibly in patients with HCV genotype 2 or 3 infection and a high CD4 cell count, for whom current HIV therapy has a higher probability of a sustained virologic response (BIIa). Avoid zidovudine, didanosine, zalcitabine, and stavudine, as well as abacavir. Alcohol should be avoided.</td>
</tr>
<tr>
<td>Opportunistic infections, including tuberculosi</td>
<td>Any, according to the “What to Start” section</td>
<td>Choice of agent will be influenced by drug interactions, especially with rifampin and rifabutin.</td>
<td>ART should be initiated as soon as possible in patients with opportunistic infections, including tuberculosis, with attention to drug interactions and the potential for immune reconstitution inflammatory syndromes (Ala). Drug interactions likely to require dose adjustments; consult drug interaction dosing references (<a href="http://www.hiv-druginteractions.org">http://www.hiv-druginteractions.org</a> and [<a href="http://hivatis.ucsf.edu/infant%5D/page-car-00-02/16,39">http://hivatis.ucsf.edu/infant]/page-car-00-02/16,39</a>)</td>
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notypic testing is recommended for all treatment-naive patients.51 For confirmed virologic failure, resistance testing is essential and should be performed while the patient is receiving the failing regimen, when possible. If the trajectory of HIV-1 RNA reduction is not optimal after a new regimen, archived mutations or minority variants may emerge. Minority variants not detected by current resistance testing have been associated with an increased risk of virologic failure; however, the assay thresholds that identify patients at greatest risk of experiencing poor outcomes have not been defined.40,115-119 Tropism testing before use of a CCR5 antagonist is essential because this class has no activity against CX chemokine receptor 4 or dual-tropic viruses.101 Improvement in tropism assay methodology may further facilitate the clinical use of CCR5 antagonists.101,120

The frequency of monitoring for ART toxicity depends on the known toxicities of specific drugs and underlying comorbidities. Monitoring may occur every 2 to 8 weeks after initiation of therapy, decreasing to every 6 to 12 months after stabilization of HIV disease.108,121 Assessment of renal function should occur before initiation and during ART, in particular when tenofovir is used, allowing avoidance, dose modification, or timely substitution of another drug when appropriate.

The recommendations and algorithms of the National Osteoporosis Foundation122 and the World Health Organization fracture risk assessment tool123,124 are useful for the assessment of risk and prevention of osteoporotic fractures; however, these tools have not been specifically validated in the HIV-infected population. Vitamin D deficiency is common in the setting of HIV infection and may be associated with ART use.123 Monitoring of vitamin D levels may be of benefit.125-127

Hepatic, cardiovascular, and renal complications may be associated with uncontrolled HIV replication. Clinical and laboratory assessment of relevant comorbid conditions should be performed before initiation of treatment and during follow-up.108,121 Cardiovascular disease risk should be assessed by available tools. The Framingham risk algorithm may be the most appropriate but may underestimate cardiovascular disease risk in the setting of HIV infection.126 Guidelines for the prevention and management of metabolic complications and noninfectious comorbidities in HIV infection are available.108,121

Therapeutic drug monitoring remains controversial.129 When assays are performed by a quality-assured laboratory, monitoring of PI and NNRTI levels may be useful in pregnant women, children, and patients with renal or liver impairment to minimize overexposure and adverse effects, manage potential drug-drug interactions, or evaluate virologic failure in the absence of resistance. As stated, HLA-B*5701 screening can identify patients at risk for abacavir-associated hypersensitivity.99

Recommendations

Plasma HIV-1 RNA levels should be monitored frequently when treatment is initiated or changed for virologic failure (AIIa) until they decrease below detection limits and regularly thereafter (BIII). Once the viral load is suppressed for a year and CD4 cell counts are stable at 350/µL or greater, viral load and CD4 cell counts can be monitored at intervals of up to 6 months in patients with dependable adherence (CIII). Baseline genotypic testing for resistance should be performed in all treatment-naive patients (AIIa) and in cases of confirmed virologic failure (Ala). HLA-B*5701 haplotype screening should be performed in any patient for whom abacavir is considered (Ala). Assessment of viral tropism is recommended before using maraviroc (Ala). Therapeutic drug monitoring is not recommended in routine care; however, selected patients might benefit from this intervention (CIII).

WHEN TO CHANGE AND WHAT TO CHANGE

Changing for Virologic Failure

The virologic goal of treatment for first- and multiple-regimen failure is to achieve a plasma HIV-1 RNA level below the limit of detection of the most sensitive assays available. With the availability of new drugs and regimens, this goal now is achievable, even in most patients with multiregimen failure.130-132 Reasons for virologic rebound after complete suppression, such as poor adherence, drug-drug interactions, concurrent infections, and recent vaccinations, should be considered before the regimen is changed. Testing for an isolated detectable viral load should be repeated to exclude measurement error or self-resolving low-level viremia.1 Stage of HIV disease, nadir and current CD4 cell count, comorbidities, treatment history, current and previous drug resistance tests, and concomitant medications with potential for interactions should be considered when the new regimen is designed. Ideally 3, but at least 2, fully active drugs should be included and drugs from new classes should be considered. The toxicities of stavudine, didanosine, and to a lesser extent zidovudine make their use problematic, and they should be used only when options are limited.

Initial Failure of NNRTI-Based Regimens. Once failure has been confirmed, an NNRTI-containing regimen should be discontinued as soon as possible to minimize the selection of additional mutations. Initial NNRTI failures traditionally have been treated with 2 active nRTIs plus a PI/r, but raltegravir, maraviroc, and etravirine now provide additional options. According to potency and high genetic barrier, the inclusion of a PI/r should be considered whenever possible, but when not possible, an agent from a new class should be considered. Treatment-experienced patients receiving etravirine and darunavir/r plus an optimized background regimen had better virologic responses than those receiving placebo plus background regimen, with comparable tolerability at 48 weeks.133

Initial Failure of PI/r Regimens. Resistance to the PI/r component does not always emerge when regimen failure is detected, allowing the same drug or another in the PI class to be used in the next regimen. For early failures, strategic sequencing of PIs should be considered. If some degree of PI resistance exists, darunavir/r is likely to be preferred over lopinavir/r or tipranavir/r because of its superior tolerability and toxicity pro-
file, as well as problematic drug interactions associated with tipranavir/r. If not previously used, an NNRTI may be included, provided that potential drug interactions are considered. Whenever possible, a new antiretroviral regimen should contain at least 2 fully active drugs.

**Multidrug (Including PI and NNRTI) Resistance.** In this setting, 3 active drugs, including new classes of agents (integrase strand transfer inhibitors or entry inhibitors), should be used. Individuals with multidrug-resistant virus usually benefit from a PI/r with activity against resistant strains, such as darunavir/r or tipranavir/r. Etravirine can be paired with darunavir/r (but not tipranavir/r) and may be of value, depending on the number of NNRTI mutations present. Enfuvirtide may be an option if no other new class can be used, despite the inconvenience of subcutaneous injection and injection site reactions. Dual-boosted PIs are not recommended. Lamivudine or emtricitabine is sometimes included to maintain the M184V mutation and decrease viral fitness, but there is no new evidence to support this approach. Another theoretically beneficial strategy is to use zidovudine to prevent the emergence of the K65R mutation in the presence of thymidine analogue mutations when using tenofovir in patients in whom nRTI-containing regimens are failing. However, no clinical benefit has been shown for this approach.

**Changes for Toxicity, Tolerability, or Convenience**

Single-agent switches to decrease toxicity, avoid drug interactions, or improve convenience and adherence are possible, provided the potency of the regimen is maintained and drug interactions are managed. Although some studies have shown maintenance of virologic suppression with PI/r monotherapy as a simplification strategy, other studies have shown higher rates of failure, especially in the central nervous system, than with a combination including 2 nRTI plus a PI/r. Therefore, PI/r monotherapy is not recommended, except in exceptional circumstances when other drugs cannot be considered for reasons of toxicity/tolerability. Delaying switches when adverse effects persist may affect adherence and facilitate the emergence of resistance.

**Simplification**

It may be desirable to switch to an equally effective regimen with fewer drugs or lower pill burden. Not all switches, even with a drug from a new class, are successful because the activity of the accompanying drugs in the regimen is a key determinant of outcome. Continuing lopinavir/r was virologically better than switching to raltegravir in patients with extensive previous 3-class ART experience and pre-existing nRTI resistance. With raltegravir, it is important to maintain a strong ART backbone, usually including a PI/r. Two smaller studies found that raltegravir was safe, well tolerated, and virologically similar when substituted for enfuvirtide in patients with multidrug-resistant HIV-1.

Once-daily darunavir 800 mg/ritonavir 100 mg was noninferior to twice-daily darunavir 600 mg/ritonavir 100 mg in an open-label study in treatment-experienced patients. Dual therapy strategies intended to take advantage of drug interactions such as the combination of unboosted atazanavir and raltegravir are still experimental and are not recommended for clinical practice. For patients with virologic suppression who were receiving a boosted or unboosted PI-based regimen, switching to a once-daily regimen containing atazanavir provided better maintenance of virologic suppression, comparable safety, and improved lipid 48 weeks compared with continued unmodified therapy.

Treatment interruptions should be avoided. Interruptions, such as those for planned surgeries or severe toxicities in patients without options for switching, should consider the different half-lives of the regimen components; drugs should be discontinued in a staggered manner (or a PI/r temporarily substituted) when an NNRTI is a component.

**Recommendations**

Maintenance of regimen potency is the objective when switching ART regimens. Virologic failure of an initial regimen (confirmed measurable viremia) should be identified and treated as early as possible with at least 2 fully active drugs (AIA) to avoid the accumulation of resistance mutations. For NNRTI failures, the new combination usually should include a PI/r or an agent from a new class (AIA) if a PI/r is not possible. Etravirine may be a useful component of a new regimen for NNRTI failure but must be supported by a potent combination including a PI/r (AIA). Depending on the resistance profile and options available, inclusion of agents from new drug classes (raltegravir or maraviroc) should be considered (BIIb). Monotherapy with a PI/r should be avoided unless other drugs cannot be considered for reasons of toxicity/tolerability (AIA).

Design of a new regimen should consider previous drug exposure, previous resistance profile, drug interactions, and history of intolerance/tolerance (CII). Treatment interruptions should be avoided, except in the context of controlled clinical trials (AIA). Elective treatment interruptions should consider the different half-lives of the regimen components, with stopping the drugs in a staggered manner when an NNRTI is a component (CII).

**CONCLUSIONS AND FUTURE DIRECTIONS**

Increasing evidence that insidious damage occurs during “asymptomatic” HIV infection underscores the potential benefit of ART, even when the risk of traditional AIDS-defining diseases is relatively low. The prominence of non-AIDS events as a major cause of morbidity and mortality in those with ongoing HIV replication suggests that early ART initiation may further improve the quality and length of life for persons living with HIV. The strategic use of newer drugs can improve tolerability, as well as provide durable and potent viral suppression in initial and subsequent therapy.

However, far too many HIV-infected persons present for medical care with advanced disease, both in wealthy and resource-limited settings. Universal voluntary HIV testing, comprehensive pre-
vination services, and early linkage to care and treatment are necessary to ensure that advances in ART are made available during earlier disease stages. Advances in ART have shown that AIDS, as traditionally defined, can be prevented. One of the greatest challenges is that full implementation of these guidelines will require addressing social and structural barriers to diagnosis and care, as well as the pervasive stigma and discrimination associated with an HIV diagnosis.

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