



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

Online article and related content current as of August 5, 2010.

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

JAMA. 2010;304(3):321-333 (doi:10.1001/jama.2010.1004)

<http://jama.ama-assn.org/cgi/content/full/304/3/321>

Supplementary material	eSupplement http://jama.ama-assn.org/cgi/content/full/304/3/321/DC1
Correction	Contact me if this article is corrected.
Citations	This article has been cited 1 time. Contact me when this article is cited.
Topic collections	HIV/AIDS; Review; Drug Therapy; Drug Therapy, Other; Immunology; Immunologic Disorders; Infectious Diseases Contact me when new articles are published in these topic areas.
CME course	Online CME course available.

Subscribe
<http://jama.com/subscribe>

Permissions
permissions@ama-assn.org
<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts
<http://jamaarchives.com/alerts>

Reprints/E-prints
reprints@ama-assn.org

Antiretroviral Treatment of Adult HIV Infection

2010 Recommendations of the International AIDS Society–USA Panel

Melanie A. Thompson, MD

Judith A. Aberg, MD

Pedro Cahn, MD

Julio S. G. Montaner, MD

Giuliano Rizzardini, MD

Amalio Telenti, MD, PhD

José M. Gatell, MD, PhD

Huldrych F. Günthard, MD

Scott M. Hammer, MD

Martin S. Hirsch, MD

Donna M. Jacobsen, BS

Peter Reiss, MD, PhD

Douglas D. Richman, MD

Paul A. Volberding, MD

Patrick Yeni, MD

Robert T. Schooley, MD

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.

 **CME available online at www.jamaarchivescme.com and questions on p 357.**

Context Recent data regarding the consequences of untreated human immunodeficiency virus (HIV) infection and the expansion of treatment choices for antiretroviral-naïve 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 $\leq 500/\mu\text{L}$, for all symptomatic patients, and those with specific conditions and comorbidities. Therapy should be considered for asymptomatic patients with CD4 cell count $>500/\mu\text{L}$. 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.

JAMA. 2010;304(3):321-333

www.jama.com

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. Data published or presented in specific scientific meetings since the last report¹

Author Affiliations are listed at the end of this article.
Corresponding Author: Melanie A. Thompson, MD, 131 Ponce de Leon Ave NE, Ste 130, Atlanta, GA 30308 (drmt@mindspring.com).

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 the 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, result-

ing 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.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/ μ L decreased mortality by 94%, and initiating it at a CD4 cell count between 351 and 500/ μ L 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/ μ L and 350 to 500/ μ L, respectively.¹²

Data from prospective observational cohorts and clinical trials demonstrate worse outcomes among patients who begin receiving ART at CD4 cell counts less than 350/ μ L 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/ μ L compared with 351 to 450/ μ L. However, this analysis included only persons who began receiving ART at less than 550/ μ L.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 recog-

nized 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.^{22,23} If ART must be interrupted, patients should be closely monitored for HBV reactivation.²⁴

Patients with HIV-hepatitis C virus (HCV) coinfection progress to end-stage liver disease more rapidly than do HCV monoinfected patients.²⁵ Clearance of HCV is associated with regression of liver fibrosis and a reduced risk of ART-related hepatotoxicity.²⁶ In one study, abacavir with ribavirin was associated with a reduced rate of sustained HCV virologic response.²⁷ Zidovudine, didanosine, and stavudine have overlapping hematologic and hepatic toxicities with current HCV therapy.²⁵ 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.²⁸

Renal disease ranges from HIV-associated nephropathy, to HIV-associated immune complex kidney disease, to

thrombotic microangiopathy. In 5 cross-sectional cohort studies, 5.5% of patients had stages 3 to 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min for more than 3 months). Older patients, blacks, persons with lower CD4 nadirs, and those with diabetes or hypertension have a higher risk of developing chronic kidney disease.^{29,30} Albuminuria and eGFR less than 60 mL/min per 1.73 m² are independently associated with an increased risk of cardiovascular events.³¹ Tenofovir is associated with a decrease in GFR and tubular dysfunction; both indinavir (about 4% of patients)³² and atazanavir³³ (uncommonly) are associated with nephrolithiasis. All nRTIs except abacavir may require dose adjustments according to the GFR.

Uncontrolled HIV infection is associated with increased cardiovascular risk.³⁴ In a multivariate analysis involving 70 357 (487 HIV-infected and 69 870 HIV-uninfected) subjects, elevated high-sensitivity C-reactive protein and HIV were independently associated with acute myocardial infarction. With both risk factors, acute myocardial infarction risk increased greater than 4-fold.³⁵ There were strong associations between overall mortality or cardiovascular disease and specific biomarkers. Although ART reduces the level of these biomarkers, they remain elevated compared with those of HIV-uninfected individuals. The clinical utility of these biomarkers for initiation or monitoring therapy is unknown. Modifiable cardiovascular risk factors should be aggressively addressed in all persons with HIV infection.

In a randomized controlled trial of when to initiate ART for patients with active opportunistic infections (excluding tuberculosis [TB]), early initiation (median, 12 days after presentation) reduced death or AIDS progression by 50% compared with beginning ART after the completion of opportunistic infection treatment.³⁶ A South African randomized controlled trial including patients with TB and HIV demonstrated that initiating ART within 2 months of begin-

ning tuberculosis treatment decreased mortality by 56% compared with initiating ART after completion of TB treatment.³⁷ 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.^{38,39}

Patients who present with symptomatic primary HIV infection may progress more rapidly than those who present without symptoms.^{40,41} Antiretroviral therapy reduces the extremely high viral loads in primary infection and may reduce transmission.^{42,43} 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.¹²

Antiretroviral therapy reduces HIV transmission.⁴⁴ Widespread use of ART during pregnancy has nearly eliminated mother-to-child transmission in the developed world.^{45,46} A meta-analysis concluded that ART also decreases the risk of HIV transmission to uninfected partners in HIV-serodiscordant heterosexual couples,⁴³ and a cohort study of 3381 heterosexual serodiscordant couples showed a 92% reduction in transmission when ART was used by the infected partner.⁴⁷ Another cohort study showed a strong association between increased ART coverage, decreased community plasma viral load, and decreased HIV incidence among injection drug users.⁴⁸ Some mathematic models suggest that more aggressive ART coverage could reduce the incidence of new HIV infections⁴⁹⁻⁵¹; some field data also support this.^{42,52}

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 (BIIa). 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, AIIIa for ≤500/μL). Treatment should be considered for asymptomatic individuals with CD4 cell counts greater than 500/μL (CIII). 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/mL¹ (AIIIa); 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 (BIII); HIV-associated kidney disease (BIIa), avoiding drugs with potential adverse effects on the kidney (tenofovir, indinavir, atazanavir), if possible (AIIIa)⁵³; 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).⁴² 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.⁵⁴

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

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

Abbreviation: HIV, human immunodeficiency virus.

^aDetails, cautions, considerations, and supporting data^{1,3-18,20-52} are described in the text. Ratings are described in the eBox (<http://www.jama.com>).

icity and tolerability, pill burden, dosing frequency, drug-drug interactions, comorbidities, and patient and practitioner preference. In the absence of overriding considerations, cost and affordability should also be considered. Current evidence supports the combination of 2 NRTIs and a potent third agent from another class (BOX). Fixed-dose formulations and once-daily regimens are generally preferred for initial therapy. The eTable presents a summary of selected clinical trial results in treatment-naive patients.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

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.⁵⁶⁻⁵⁸ 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.^{59,60} 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. Abacavir plus lamivudine also was associated with more lipid abnormalities.^{61,62} 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.^{63,64} 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 coinfecting 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/^{61,62} 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.¹⁷ 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

Box. Recommended Components of the Initial Antiretroviral Regimen^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^b to reduce risk of abacavir hypersensitivity
- Abacavir may be associated with increased cardiovascular risk

Key Third Agent

Recommended

Efavirenz^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

Atazanavir/r^b

- PI/r class
- Once daily
- Widely prescribed when PI/r is chosen for initial therapy
- Leaves options for future regimens
- Less lipogenic potential than lopinavir/r
- Hyperbilirubinemia, need for acid-reducing agents, and risk of nephrolithiasis influence choice

Darunavir/r^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 effi-

cacy in patients with treatment experience, and multidrug-resistant virus influence choice

Raltegravir^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.

^aDetails, cautions, considerations, and supporting data^{1,17,55-105} are described in the text.

^bBased on extensive clinical experience.

^cBased on antiviral efficacy and tolerability comparable to that of key third agents but more limited experience in treatment-naive patients.

with CD4 cell counts less than 250/ μ L and 400/ μ L, respectively.⁷⁷ Nevirapine was similar virologically to lopinavir/r (again, each with tenofovir/emtricitabine) in a randomized trial of 500 Afri-

can women with CD4 cell counts less than 200/ μ L.⁷⁸ However, drug discontinuation because of adverse events was higher among nevirapine recipients.^{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/ μ L (women) or less than

400/ μ L (men).⁸¹ 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.⁸² 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.⁸³ 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.^{84,85} 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,³³ and the eGFR may decrease when atazanavir is combined with tenofovir.⁸⁶ Unboosted atazanavir should not be used with tenofovir.⁸⁷ 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.⁸⁸

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.⁸⁹ Grade 2 to 4 adverse events, primarily diarrhea, were more frequent in the lopinavir/r arm.⁹⁰ Darunavir/r is considered by many as less attractive in initial therapy because it is particularly useful for patients with PI-resistant virus.

Lopinavir/r demonstrates lower virologic efficacy but better CD4 response and fewer emergent resistance mutations than efavirenz.^{69,72,73} For initial

therapy, once-daily and twice-daily lopinavir/r in combination with tenofovir plus emtricitabine achieved comparable rates of plasma HIV-1-RNA levels less than 50 copies/mL at 48 weeks,⁹¹ with similar rates of moderate to severe drug-related diarrhea. Other major adverse effects of lopinavir/r include insulin resistance and hyperlipidemia.

Twice-daily fosamprenavir/r and lopinavir/r, both administered with abacavir plus lamivudine, had comparable rates of virologic suppression and adverse events at 48 and 144 weeks.⁹² Once-daily vs twice-daily fosamprenavir/r did not differ in rates of virologic suppression.⁹³

Saquinavir/r was compared with lopinavir/r, both with tenofovir plus emtricitabine, resulting in rates of viral suppression at 48 weeks of about 65% for each regimen; however, the statistical power of this study was limited by small sample size and short length of follow-up.⁹⁴ Triglyceride levels were higher in the lopinavir/r arm. Although this was possibly a class effect, the Food and Drug Administration has issued a warning of a potential risk for QT-interval prolongation with saquinavir/r.⁹⁵

Hepatic transaminase elevations can occur with any of the above regimens,⁹⁶ especially in patients with underlying liver disease. Cumulative exposure to indinavir/r, lopinavir/r, and fosamprenavir/r (but not saquinavir/r) has also been associated with an increased risk of cardiovascular events.^{63,64,97} If possible, these drugs are best avoided in patients with elevated cardiovascular risk. Data concerning cardiovascular risk associated with atazanavir/r or darunavir/r are pending.

Integrase Strand Transfer Inhibitors

Raltegravir and efavirenz, each combined with tenofovir and emtricitabine, showed similar high virologic efficacy during 192 weeks.^{71,98,99} Raltegravir is well tolerated and has a favorable lipid and drug interaction profile; however, it is dosed twice daily and has a relatively low genetic barrier for selection of resistance mutations.¹⁰⁰ Raltegravir is considered by some as less attractive for initial therapy because it is particularly useful for patients with drug-resistant virus.

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.¹⁰¹ 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.¹⁰² 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.^{101,103-105} 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 (A1a). Neither saquinavir/r nor unboosted PIs, including atazanavir, are recommended for initial therapy (B1a). 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) (B1). 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.¹⁰⁶ 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.^{107,108} 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.¹⁰⁹ 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.¹¹⁰

Changes in assay methodology may result in detectable viral load in individuals with previously undetectable viremia.^{111,112} Detection artifacts have also been attributed to specific plasma processing practices.¹¹³ New assays may soon be available with a lower limit of 20 copies/mL; however, the clinical implications of viremia between 20 and 50 copies/mL 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%.^{75,76,114} Baseline ge-

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

Condition	Regimen Components		Considerations
	Possible Backbone Drugs	Third Agent	
High atherosclerotic cardiovascular risk	Emtricitabine, lamivudine, tenofovir	Efavirenz, nevirapine, atazanavir/r, raltegravir	Initiation of ART, regardless of CD4 cell count, is recommended. ³⁴ If possible avoid abacavir, fosamprenavir/r, indinavir/r, lopinavir/r because of an associated increased risk of cardiovascular events. ^{53,57}
Chronic kidney disease	Abacavir, ^b emtricitabine, lamivudine; avoid tenofovir (glomerular and tubular toxicity), atazanavir, and indinavir (nephrolithiasis)	Efavirenz, raltegravir, nevirapine, maraviroc, PI/r	Initiate ART regardless of CD4 cell count (B1a). Avoid potentially nephrotoxic drugs (A1a). ⁵³ When potentially nephrotoxic drugs must be used, monitor renal function closely. For patients with reduced estimated glomerular filtration rate, dose adjustment for drugs with renal metabolism (emtricitabine, lamivudine, tenofovir, maraviroc) should be considered.
Chronic HBV infection	Emtricitabine, lamivudine, tenofovir. Use 2 HBV-active drugs. Do not use abacavir or lamivudine alone for treatment of HBV in coinfecting patients.	Efavirenz, raltegravir, PI/r should be monitored for hepatotoxicity. Avoid nevirapine except for women with CD4 <250/μL and men with <400/μL. Maraviroc should be used with caution in patients with liver disease.	ART that includes tenofovir/emtricitabine should be used irrespective of CD4 cell count ²⁰ (B1a). Monitor alanine aminotransferase after ART initiation and after withdrawal of suppressive therapy. ²²⁻²⁴ In patients with moderate to severe liver impairment, dose adjustment for drugs metabolized by the liver should be considered. Alcohol should be avoided.
Chronic HCV infection requiring therapy	Emtricitabine, lamivudine, tenofovir	Efavirenz, raltegravir, PI/r should be monitored for hepatotoxicity. Avoid nevirapine except for women with CD4 <250/μL and men with <400/μL. Maraviroc should be used with caution in patients with liver disease.	ART should generally be initiated first in all patients with HCV coinfection regardless of CD4 cell count to slow liver disease progression (B1a), except possibly in patients with HCV genotype 2 or 3 infection and a high CD4 cell count, for whom current HCV therapy has a higher probability of a sustained virologic response ^{26,28} (B111). Avoid zidovudine, didanosine, zalcitabine, and stavudine, as well as abacavir. ^{25,27} Alcohol should be avoided by all coinfecting patients.
Pregnant women	Complete recommendations for the use of antiviral therapy in pregnant women are available at http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf , and http://www.europeanaidssociety.org/guidelines.asp . ^{17,18}		ART is recommended to prevent the transmission of the virus to the fetus or infant (A1a). Efavirenz should generally be avoided, especially in the first trimester of pregnancy (teratogenic effect).
Opportunistic infections, including tuberculosis	Any, according to the "What to Start" section	Choice of agent will be influenced by drug interactions, especially with rifampin and rifabutin.	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 (A1a). ^{36,37} Drug interactions likely to require dose adjustments; consult drug interaction dosing references (http://www.hiv-druginteractions.org , and http://hivinsite.ucsf.edu/insite?page=ar-00-02). ^{38,39}

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; PI, protease inhibitor; /r, ritonavir boosted.

^aDetails, cautions, considerations, and supporting data are described in the text. Levels of evidence are described in the eBox (available at <http://www.jama.com>).

^bIn HLA B*5701-negative patients; has been associated with increased risk of myocardial infarction. Lower efficacy in patients with >100 000 copies/mL of HIV RNA at baseline (see text).

notypic testing is recommended for all treatment-naïve patients.⁸¹ 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 tool^{123,124} 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.¹²⁵ 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.¹²⁸ 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.⁵⁹

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-naïve patients (AIIa) and in cases of confirmed virologic failure (AIIa). HLA-B*5701 haplotype screening should be performed in any patient for whom abacavir is considered (AIIa). Assessment of viral tropism is recommended before using maraviroc (AIIa). 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 viral 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.¹ 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.¹³⁴ 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.¹³⁵

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,¹³⁶ other studies have shown higher rates of failure, especially in the central nervous system,¹³⁷ than with a combination including 2 nRTI plus a PI/r.^{138,139} 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.¹⁴⁰ 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.^{141,142}

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.¹⁴³ 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 lipids through 48 weeks compared with continued unmodified therapy.¹⁴⁴

Treatment interruptions should be avoided.¹ 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.¹⁴⁵

Recommendations

Maintenance of regimen potency is the objective when switching ART regi-

mens. 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 (A1a) 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 (A1a) 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 (A1a). Depending on the resistance profile and options available, inclusion of agents from new drug classes (raltegravir or maraviroc) should be considered (B11b). Monotherapy with a PI/r should be avoided unless other drugs cannot be considered for reasons of toxicity/tolerability (A1a).

Design of a new regimen should consider previous drug exposure, previous resistance profile, drug interactions, and history of intolerance/toxicity (C111). Treatment interruptions should be avoided, except in the context of controlled clinical trials (A1a). 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 (C111).

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-

vention 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.

Author Affiliations: AIDS Research Consortium of Atlanta, Atlanta, Georgia (Dr Thompson); University of California San Diego, La Jolla (Dr Schooley); New York University School of Medicine, New York (Dr Aberg); Hospital Juan Fernandez/University of Buenos Aires Medical School and Fundacion Huesped, Argentina (Dr Cahn); Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain (Dr Gatell); University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, University of Zurich, Zurich, Switzerland (Dr Günthard); Columbia University College of Physicians and Surgeons, New York, New York (Dr Hammer); Harvard Medical School, Boston, Massachusetts (Dr Hirsch); International AIDS Society—USA, San Francisco, California (Ms Jacobsen); BC-Centre for Excellence in HIV/AIDS, Providence Health Care and University of British Columbia, Vancouver, Canada (Dr Montaner); Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Dr Reiss); University of California San Diego and Veterans Affairs San Diego Healthcare System (Dr Richman); Luigi Sacco Hospital, Milan, Italy (Dr Rizzardini); University Hospital of Lausanne, Lausanne, Switzerland (Dr Telenti); University of California San Francisco and San Francisco Veterans Affairs Medical Center (Dr Volberding); and Hôpital Bichat-Claude Bernard and Xavier Bichat Medical School, Paris, France (Dr Yeni).

Author Contributions: *Study concept and design:* Thompson, Aberg, Cahn, Rizzardini, Telenti, Gatell, Günthard, Hammer, Hirsch, Jacobsen, Reiss, Richman, Volberding, Yeni, Schooley.

Acquisition of data: Thompson, Aberg, Cahn, Rizzardini, Telenti, Hammer, Volberding, Schooley.

Analysis and interpretation of data: Thompson, Aberg, Cahn, Montaner, Rizzardini, Telenti, Gatell, Günthard, Hammer, Hirsch, Reiss, Richman, Volberding, Yeni, Schooley.

Drafting of the manuscript: Thompson, Aberg, Cahn, Rizzardini, Telenti, Günthard, Hirsch, Jacobsen, Reiss, Richman, Volberding, Schooley.

Critical revision of the manuscript for important intellectual content: Thompson, Aberg, Cahn, Montaner, Rizzardini, Telenti, Gatell, Günthard, Hammer, Hirsch, Reiss, Richman, Volberding, Yeni, Schooley.

Obtained funding: Jacobsen, Volberding.

Administrative, technical, or material support: Montaner, Günthard, Hammer, Jacobsen, Volberding. *Study supervision:* Thompson, Cahn, Telenti, Hammer, Hirsch, Jacobsen, Schooley.

Financial Disclosures: Dr Thompson reported receiving research grants awarded to AIDS Research Consortium of Atlanta from Abbott Laboratories, Avexa, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, GeoVax, Katketsuken, Koronis Pharmaceuticals, Merck Research Laboratories, Myriad, Ora-Sure, Panacos Pharmaceuticals (now Myriad), Pfizer, Progenics Pharmaceuticals (now Myriad), Pfizer, Progenics Pharmaceuticals, Roche Laboratories, Roche Molecular Systems, Serono, Theratechnologies Tibotec Therapeutics, Tobira Therapeutics, Trimeris, and VaxGen; has served on the

scientific advisory boards or as a clinical trial design consultant for Chimerix, GeoVax, GlaxoSmithKline, Panacos Pharmaceuticals, Progenics Pharmaceuticals, and Tibotec Therapeutics; has received honoraria for scientific lectures from GlaxoSmithKline and Serono; and has served on data and safety monitoring boards for Tibotec Therapeutics. Dr Aberg reported serving as a scientific advisor to Abbott Laboratories, Boehringer Ingelheim Pharmaceutical, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, Tibotec Therapeutics, and ViiV Healthcare; has received grants and research support from Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Schering-Plough, Theratechnologies, Tibotec Therapeutics, Virco Lab, and Wyeth; and has received honoraria from Abbott Laboratories, Bristol-Myers Squibb, and Gilead Sciences. Dr Cahn reported serving on the advisory boards for Avexa, Gilead Sciences, GlaxoSmithKline, Myriad Genetics, Merck, Pfizer, Pharmasset, Schering-Plough, and Tibotec Therapeutics; has served as an investigator for Avexa, Boehringer Ingelheim Pharmaceuticals, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Pharmasset, Roche Laboratories, Schering-Plough, and Tibotec Therapeutics; and has received honoraria for speaking engagements from Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Merck, Pfizer, and Tibotec Therapeutics. Dr Montaner reported receiving research grants from, and served as an ad hoc advisor or consultant to, Abbott Laboratories, Argos Therapeutics, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Cato Research Canada, ConjuChem Biotech, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Johnson & Johnson, Merck Canada, Merck Frosst Laboratories, Pfizer Canada, Serono, Theratechnologies, and Tibotec Pharmaceuticals and has served on an endpoint adjudication committee for Schering-Plough. Dr Rizzardini reported receiving research grants from Gilead Sciences and Merck Sharp & Dohme. Dr Telenti reported receiving research grants or honoraria for lectures from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, and GlaxoSmithKline. Dr Gatell reported receiving research grants or honoraria for serving on advisory boards or for lectures from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharpe & Dohme, Pfizer, GlaxoSmithKline, Roche Laboratories, Theratechnologies, Tibotec Therapeutics, Tobira Therapeutics, and Virco Lab. Dr Günthard reported serving as a consultant and medical advisor for Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals, Gilead Sciences, GlaxoSmithKline, Pfizer, Tibotec Therapeutics, and ViiV Healthcare and has received unrestricted research and educational grants from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Pfizer. Dr Hammer reported serving on a scientific or clinical advisory boards for Merck, Progenics Pharmaceuticals, TaiMed Biologics, Tibotec Therapeutics, and Wyeth; has received clinical research contracts from Merck; and has served on data and safety monitoring boards and committees for Bristol-Myers Squibb and on the board of directors of SIGA Pharmaceuticals. Dr Hirsch reported serving on data and safety monitoring boards for Merck and TaiMed Biologics. Dr Reiss reported serving as a scientific advisor to Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Theratechnologies, Tibotec Therapeutics, and Tobira Therapeutics; has served on data and safety monitoring boards and endpoint adjudication committees for Tibotec Therapeutics; has received honoraria for speaking engagements at scientific conferences from Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, and Theratechnologies; and has received research support from Gilead Sciences, ViiV Healthcare, and Boehringer Ingelheim Pharmaceuti-

cals. Dr Richman reported being a consultant to Anadys Pharmaceuticals, Biota, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Chimerix, Gen-Probe, Gilead Sciences, Idenix Pharmaceuticals, Koronis Pharmaceuticals, Merck, Monogram Biosciences, Myriad Genetics, Pfizer, Roche, Theraclone Sciences, and Tobira Therapeutics; has served on an endpoint adjudication committee for Schering-Plough; has been the recipient of a research grant from Merck; and has been a stock options holder of Chimerix and Idenix Pharmaceuticals. Dr Volberding reported serving on data and safety monitoring boards for Merck and TaiMed Biologics and on an endpoint adjudication committee for Schering-Plough; has provided paid expert testimony for commercial firms; has served on scientific or clinical advisory boards for Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, and Tobira Therapeutics; and has been the recipient of service grants for, or held contracts from, GlaxoSmithKline Italy. Dr Yeni reported receiving scientific grants from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, Merck, and Roche Laboratories. Dr Schooley reported serving as a consultant to Achillion Pharmaceuticals, Anadys Pharmaceuticals, Ardea Biosciences, Gilead Sciences, GlaxoSmithKline, Inhibitex, iTherX, Johnson & Johnson, LabCorp, Merck, Myriad Biosciences, Pfizer, TaiMed Biologics, Tanox, Tobira Therapeutics, Vertex Pharmaceuticals, and Vical; has received grants from Gilead Sciences and Pfizer; and has stock options for Achillion Pharmaceuticals.

Funding/Support: This work was funded by the International AIDS Society—USA. Panel members serve in volunteer capacities (ie, are not compensated). No private sector or government funding was used to support the effort. The International AIDS Society—USA has received grants for selected CME activities (unrelated to guidelines development) from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Roche Laboratories, Tibotec Therapeutics, and ViiV Healthcare. Grants are pooled such that no single company supports any single effort.

Role of the Sponsor: The International AIDS Society—USA determined the need for updated recommendations, selected the panel members, and provided administrative oversight and financial support.

Online-Only Material: The eTable, eBox, and eFigure are available at <http://www.jama.com>.

Additional Contributions: We thank Michelle Tayag Valderama, BS, who was compensated as an employee of the International AIDS Society—USA, for administrative support.

REFERENCES

1. Hammer SM, Eron JJ Jr, Reiss P, et al; International AIDS Society—USA. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society—USA panel. *JAMA*. 2008;300(5):555-570.
2. Carpenter CCJ, Fischl MA, Hammer SM, et al; International AIDS Society—USA. Antiretroviral therapy for HIV infection in 1996. *JAMA*. 1996;276(2):146-154.
3. Harrison KM, Song R, Zhang X. Life expectancy after HIV diagnosis based on national HIV surveillance data from 25 states, United States. *J Acquir Immune Defic Syndr*. 2010;53(1):124-130.
4. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med*. 2007;146(2):87-95.
5. Bhaskaran K, Hamouda O, Sannes M, et al; CASCADE Collaboration. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. 2008;300(1):51-59.
6. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analy-

- sis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299.
7. Neuhaus J, Angus B, Kowalska JD, et al; INSIGHT SMART and ESPRIT study groups. Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. *AIDS*. 2010;24(5):697-706.
 8. Anis AH, Nosyk B, Sun H, et al; OPTIMA Team. Quality of life of patients with advanced HIV/AIDS: measuring the impact of both AIDS-defining events and non-AIDS serious adverse events. *J Acquir Immune Defic Syndr*. 2009;51(5):631-639.
 9. Palella F, Armon C, Buchacz K, et al. CD4 at HAART initiation predicts long-term CD4 responses and mortality from AIDS and non-AIDS causes in the HIV outpatients study. In: *17th Annual Canadian Conference on HIV/AIDS Research*. San Francisco, CA: CROI; 2010. Abstract 983.
 10. Kitahata MM, Gange SJ, Abraham AG, et al; NA-ACCORD Investigators. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826.
 11. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50(10):1387-1396.
 12. HIV-CAUSAL Collaboration. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*. 2010;24(1):123-137.
 13. Sterne JA, May M, Costagliola D, et al; When To Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009;373(9672):1352-1363.
 14. Ferry T, Raffi F, Collin-Filleul F, et al; ANRS CO8 (APROCO-COPILOTE) Study Group. Uncontrolled viral replication as a risk factor for non-AIDS severe clinical events in HIV-infected patients on long-term antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009;51(4):407-415.
 15. Monforte A, Abrams D, Pradier C, et al; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008;22(16):2143-2153.
 16. Hargrove JW, Humphrey JH; ZVITAMBO Study Group. Mortality among HIV-positive postpartum women with high CD4 cell counts in Zimbabwe. *AIDS*. 2010;24(3):F11-F14.
 17. Perinatal HIV Guidelines Working Group. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States—April 29, 2009. <http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed February 26, 2010.
 18. European AIDS Clinical Society. European guidelines for clinical management and treatment of HIV infected adults in Europe. <http://www.europeanaidsclinicalociety.org/guidelines.asp>. Accessed March 18, 2010.
 19. Thio CL, Seaberg EC, Skolasky R Jr, et al; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926.
 20. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-662.
 21. Pessôa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfecting patients receiving lamivudine as part of antiretroviral therapy. *AIDS*. 2008;22(14):1779-1787.
 22. Bellini C, Keiser O, Chave JP, et al; Swiss HIV Cohort Study. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med*. 2009;10(1):12-18.
 23. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis*. 1999;28(5):1032-1035.
 24. Dore GJ, Soriano V, Rockstroh J, et al; SMARTINSIGHT study group. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfecting patients following antiretroviral therapy interruption. *AIDS*. 2010;24(6):857-865.
 25. Sulkowski MS. Management of hepatic complications in HIV-infected persons. *J Infect Dis*. 2008;197(suppl 3):S279-S293.
 26. Labarga P, Soriano V, Vispo ME, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis*. 2007;196(5):670-676.
 27. Laufer N, Laguno M, Perez I, et al. Abacavir does not influence the rate of virological response in HIV-HCV-coinfecting patients treated with pegylated interferon and weight-adjusted ribavirin. *Antivir Ther*. 2008;13(7):953-957.
 28. Seden K, Back D, Khoo S. New directly acting antivirals for hepatitis C: potential for interaction with antiretrovirals. *J Antimicrob Chemother*. 2010;65(6):1079-1085.
 29. Freedman BI, Hicks PJ, Bostrom MA, et al. Polymorphisms in the non-muscle myosin heavy chain 9 gene (MYH9) are strongly associated with end-stage renal disease historically attributed to hypertension in African Americans. *Kidney Int*. 2009;75(7):736-745.
 30. Post FA, Holt SG. Recent developments in HIV and the kidney. *Curr Opin Infect Dis*. 2009;22(1):43-48.
 31. Choi AI, Li Y, Deeks SG, Grunfeld C, et al. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation*. 2010;121(5):651-658.
 32. Kopp JB, Miller KD, Mican JA, et al. Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med*. 1997;127(2):119-125.
 33. Chan-Tack KM, Truffa MM, Struble KA, Birmkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS*. 2007;21(9):1215-1218.
 34. Phillips AN, Carr A, Neuhaus J, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther*. 2008;13(2):177-187.
 35. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. *J Acquir Immune Defic Syndr*. 2009;51(3):268-273.
 36. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575.
 37. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706.
 38. Drug Interactions HIV. Drug interactions charts. <http://www.hiv-druginteractions.org/>. Accessed March 30, 2010.
 39. HIV InSite. Database of antiretroviral drug interactions. <http://hivinsite.ucsf.edu/inSite?page=ar-00-02>. Accessed March 30, 2010.
 40. Boltz V, Zheng Y, Lockman S, et al. NNRTI-resistant variants detected by allele-specific PCR predict outcome of NVP-containing ART in women with prior exposure to sNVP: results from the OCTANE/A5208 Study. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 154.
 41. Markowitz M, Vaida F, Hare CB, et al. The virologic and immunologic effects of cyclosporine as an adjunct to antiretroviral therapy in patients treated during acute and early HIV-1 infection. *J Infect Dis*. 2010;201(9):1298-1302.
 42. Rieder P, Joos B, von Wyl V, et al; Swiss HIV Cohort Study. HIV-1 transmission after cessation of early antiretroviral therapy among men having sex with men. *AIDS*. 2010;24(8):1177-1183.
 43. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS*. 2009;23(11):1397-1404.
 44. Montaner JS, Hogg R, Wood E, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet*. 2006;368(9534):531-536.
 45. von Linstow ML, Rosenfeld V, Lebech AM, et al. Prevention of mother-to-child transmission of HIV in Denmark, 1994-2008. *HIV Med*. doi:10.1111/j.1468-1293.2009.00811.x.
 46. Dabis F, Newell ML, Hirschel B. HIV drugs for treatment, and for prevention. *Lancet*. 2010;375(9731):2092-2098.
 47. Donnell D, Mimiaga MJ, Mayer K, Chesney M, Koblin B, Coates T. Use of non-occupational post-exposure prophylaxis does not lead to an increase in high risk sex behaviors in men who have sex with men participating in the EXPLORE trial. *AIDS Behav*. doi:10.1007/s10461-010-9712-1.
 48. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ*. 2009;338:1649.
 49. Lima VD, Johnston K, Hogg RS, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. *J Infect Dis*. 2008;198(1):59-67.
 50. Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373(9657):48-57.
 51. Lima VD, Hogg RS, Montaner JSG. Expanding HAART treatment to all currently eligible individuals under the 2008 IAS-USA Guidelines in British Columbia, Canada. *PLoS One*. 2010;5(6):e10991.
 52. Montaner JG, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada. *Lancet*. doi:10.1016/S0140-6736(10)60936-1.
 53. Kirk O, Mocroft A, Reiss P, et al. Chronic kidney disease and exposure to ART in a large cohort with long-term follow-up: the EuroSIDA study. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 107LB.
 54. Gardner LI, Marks G, O'Daniels CM, et al. Implementation and evaluation of a clinic-based behavioral intervention: positive steps for patients with HIV. *AIDS Patient Care STDs*. 2008;22(8):627-635.
 55. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis*. 2006;42(2):283-290.
 56. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther*. 2008;83(2):265-272.
 57. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS*. 2009;23(15):1971-1975.
 58. Goicoechea M, Liu S, Best B, et al; California Collaborative Treatment Group 578 Team. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 2008;197(1):102-108.
 59. Mallal S, Phillips E, Carosi G, et al; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
 60. Saag M, Balu R, Phillips E, et al; Study of Hypersensitivity to Abacavir and Pharmacogenetic Evalua-

- tion Study Team. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118.
61. Sax PE, Tierney C, Collier AC, et al; AIDS Clinical Trials Group Study A5202 Team. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240.
62. Daar E, Tierney C, Fischl M, et al. ACTG 5202: final results of ABC/3TC or TDF/FTC with either EFV or ATV/r in treatment-naive HIV-infected patients. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 59LB.
63. Sabin CA, Worm SW, Weber R, et al; D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426.
64. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330.
65. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr*. 2009;51(1):20-28.
66. Aberg JA, Ribaud H. Cardiac risk: not so simple. *J Infect Dis*. 2010;201(3):315-317.
67. Cooper DA; Altair Study Group. Safety and efficacy of three different combination antiretroviral regimens as initial therapy for HIV infection: week 48 data from a randomised, open-label study. In: *5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention*. Cape Town, South Africa: International AIDS Society; 2009. Abstract LBPE09.
68. Cassetti I, Madruga JV, Etzel A, et al. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naive patients through seven years. In: *17th Annual International AIDS Conference*. Mexico City, Mexico: International AIDS Society; 2008. Abstract TUPE0057.
69. Riddler SA, Haubrich RH, DiRienzo AG, et al; AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106.
70. Young J, Bucher HC, Gunthard HF, et al; Swiss HIV Cohort Study. Virological and immunological responses to efavirenz or boosted lopinavir as first-line therapy for patients with HIV. *Antivir Ther*. 2009;14(6):771-779.
71. Lennox JL, DeJesus E, Lazzarin A, et al; STARTMRK investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806.
72. von Wyl V, Yerly S, Böni J, et al; for the Swiss HIV Cohort Study. Emergence of HIV-1 drug resistance in previously untreated patients initiating combination antiretroviral treatment: a comparison of different regimen types. *Arch Intern Med*. 2007;167(16):1782-1790.
73. Sierra-Madero J, Villasis-Keever A, Méndez P, et al. Prospective, randomized, open label trial of Efavirenz vs Lopinavir/Ritonavir in HIV+ treatment-naive subjects with CD4+ <200 cells/mm³ in Mexico. *J Acquir Immune Defic Syndr*. 2010;53(5):582-588.
74. Wheeler W, Ziebell R, Zabina H, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, US—2006. *AIDS*. 2010;24:1203-1212.
75. Vercauteren J, Wensing AM, van de Vijver DA, et al. Transmission of drug-resistant HIV-1 is stabilizing in Europe. *J Infect Dis*. 2009;200(10):1503-1508.
76. Kim D, Wheeler W, Ziebell R, et al. Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1 infected persons, United States, 2007. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 580.
77. Soriano V, Koppe S, Migrone H, et al. Prospective randomised comparison of nevirapine and atazanavir /ritonavir both combined with tenofovir DF /emtricitabine in treatment-naive HIV-1 infected patients: ARTEN Study week 48 results. In: *5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention*. Cape Town, South Africa: International AIDS Society; 2008. Abstract LBPE07.
78. McIntyre J, Hughes M, Mellors J, et al. Efficacy of ART with NVP+TDF/FTC vs LPV/r+TDF/FTC among antiretroviral-naive women in Africa: OCTANE Trial 2/ACTG A5208. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 153LB.
79. Rey D, Hoen B, Chavanet P, et al. High rate of early virological failure with the once-daily tenofovir /lamivudine/nevirapine combination in naive HIV-1-infected patients. *J Antimicrob Chemother*. 2009;63(2):380-388.
80. Lepadula G, Costarelli S, Quiros-Roldan E, et al. Risk of early virological failure of once-daily tenofovir-emtricitabine plus twice-daily nevirapine in antiretroviral therapy-naive HIV-infected patients. *Clin Infect Dis*. 2008;46(7):1127-1129.
81. Hirsch MS, Günthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. 2008;47(2):266-285.
82. Kesselring AM, Wit FW, Sabin CA, et al; Nevirapine Toxicity Multicohort Collaboration. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS*. 2009;23(13):1689-1699.
83. Malan DR, Krantz E, David N, Wirtz V, Hammond J, McGrath D; 089 Study Group. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. 2008;47(2):161-167.
84. Molina JM, Andrade-Villanueva J, Echevarria J, et al; CASTLE Study Team. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646-655.
85. Molina J, Andrade-Villanueva J, Echeverria J; CASTLE Study Team. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96 week efficacy and safety results of the CASTLE study. *JAIDS*. 2010;53:323-332.
86. Misovich SJ, Fisher JD, Fisher WA. Close relationships and elevated HIV risk behavior. *Rev Gen Psychol*. 1997;1(1):72-107.
87. Le Tiec C, Barrail A, Goujard C, Taburet AM. Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet*. 2005;44(10):1035-1050.
88. Klein CE, Chiu YL, Cai Y, et al. Effects of acid-reducing agents on the pharmacokinetics of lopinavir /ritonavir and ritonavir-boosted atazanavir. *J Clin Pharmacol*. 2008;48(5):553-562.
89. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS*. 2009;23(13):1679-1688.
90. Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir /ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389-1397.
91. Gathe J, Da Silva B, Cohen DE, et al. A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naive subjects through 48 weeks. *JAIDS*. 2009;15:474-481.
92. Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir /lamivudine over 144 weeks. *HIV Clin Trials*. 2009;10(2):76-87.
93. Carosi L, Lazzarin A, Stellbrink H, et al. Study of once-daily versus twice-daily fosamprenavir plus ritonavir administered with abacavir/lamivudine once daily in antiretroviral-naive HIV-1-infected adult subjects. *HIV Clin Trials*. 2009;10(6):356-367.
94. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr*. 2009;50(4):367-374.
95. US Food and Drug Administration. FDA drug safety communication: ongoing safety review of saquinavir and possible association with abnormal heart rhythms. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm201221.htm>. Published February 23, 2010. Accessed May 18, 2010.
96. Haubrich RH, Riddler SA, DiRienzo AG, et al; AIDS Clinical Trials Group (ACTG) A5142 Study Team. Metabolic outcomes in a randomized trial of nucleoside, non-nucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. 2009;23(9):1109-1118.
97. Lang S, Mary-Krause M, Cotte L, et al. Impact of specific nRTI and PI exposure on the risk of myocardial infarction: a case-control study nested within FHDH ANRS CO4. In: *16th Conference on Retroviruses and Opportunistic Infections*. Montreal, Canada: CROI; 2009. Abstract 43LB.
98. Lennox J, DeJesus E, Berger DS, et al. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *JAIDS*. doi: 10.1097/QAI.0b013e3181da1287.
99. Gotuzzo E, Nguyen BY, Markowitz M, et al. Sustained antiretroviral efficacy of raltegravir after 192 weeks of combination ART in treatment-naive HIV-1 infected patients. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 514.
100. Canducci F, Sampaolo M, Marinuzzi MC, et al. Dynamic patterns of human immunodeficiency virus type 1 integrase gene evolution in patients failing raltegravir-based salvage therapies. *AIDS*. 2009;23(4):455-460.
101. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis*. 2010;201(6):803-813.
102. Heera J, Iye P, Botes M, et al. The MERIT study of maraviroc in antiretroviral-naive patients with R5 HIV-1: 96-week results. In: *5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention*. Cape Town, South Africa: International AIDS Society; 2009. Abstract TUAB103.
103. Swenson LC, Moores A, Low AJ, et al. Improved detection of CXCR4-using HIV by V3 genotyping: application of population-based and "deep" sequencing to plasma RNA and proviral DNA. *JAIDS*. doi: 10.1097/QAI.0b013e3181d0558f.
104. McGovern R, Dong W, Zhong X, et al. Population-based sequencing of the V3-loop is comparable to the enhanced sensitivity profile assay (ESTA) in predicting virologic response to maraviroc (MVC) of treatment-naive patients in the MERIT Trial. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 92.
105. Swenson L, Dong W, Mo T, et al. Large-scale ap-

- plication of deep sequencing using 454 technology to HIV tropism screening. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 545.
106. Gupta RK, Hill A, Sawyer AW, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2009;9(7):409-417.
107. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. *MMWR Recomm Rep*. 2009;58(RR-4):1-207, quiz CE1-CE4.
108. Aberg JA, Kaplan JE, Libman H, et al; HIV Medicine Association of the Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(5):651-681.
109. Reekie J, Mocroft A, Sambatakou H, et al; EuroSIDA Study Group. Does less frequent routine monitoring of patients on a stable, fully suppressed cART regimen lead to an increased risk of treatment failure? *AIDS*. 2008;22(17):2381-2390.
110. Reekie J, Mocroft A, Ledergerber B, et al; for the EuroSIDA Study Group. History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change. *HIV Med*. 2010. doi:10.1111/j.1468-1293.2009.00816.x.
111. Lima VD, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr*. 2009;51(1):3-6.
112. Pas S, Rossen JW, Schoener D, et al. Performance evaluation of the new Roche COBAS AmpliPrep COBAS TaqMan HIV-1 test version 2.0 for the quantification of human immunodeficiency virus type 1 RNA. *J Clin Microbiol*. 2010;48(4):1195-1200.
113. Rebeiro PF, Kheshti A, Bebawy SS, et al. Increased detectability of plasma HIV-1 RNA after introduction of a new assay and altered specimen-processing procedures. *Clin Infect Dis*. 2008;47(10):1354-1357.
114. Yerly S, von Wyl V, Ledergerber B, et al; Swiss HIV Cohort Study. Transmission of HIV-1 drug resistance in Switzerland: a 10-year molecular epidemiology survey. *AIDS*. 2007;21(16):2223-2229.
115. Halvas EK, Wiegand A, Boltz VF, et al. Low frequency nonnucleoside reverse-transcriptase inhibitor-resistant variants contribute to failure of efavirenz-containing regimens in treatment-experienced patients. *J Infect Dis*. 2010;201(5):672-680.
116. Paredes R, Lalama CM, Ribaldo HJ, et al; AIDS Clinical Trials Group (ACTG) A5095 Study Team. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. 2010;201(5):662-671.
117. Heneine W. When do minority drug-resistant HIV-1 variants have a major clinical impact? *J Infect Dis*. 2010;201(5):647-649.
118. Metzner KJ, Giulieri SG, Knoepfel SA, et al. Minority quasispecies of drug-resistant HIV-1 that lead to early therapy failure in treatment-naïve and -adherent patients. *Clin Infect Dis*. 2009;48(2):239-247.
119. Mackie NE, Phillips AN, Kaye S, Booth C, Geretti AM. Antiretroviral drug resistance in HIV-1-infected patients with low-level viremia. *J Infect Dis*. 2010;201(9):1303-1307.
120. Bozek K, Thielen A, Sierra S, Kaiser R, Lengauer T. V3 loop sequence space analysis suggests different evolutionary patterns of CCR5- and CXCR4-tropic HIV. *PLoS One*. 2009;4(10):e7387.
121. European AIDS Clinical Society. Guidelines on prevention and management of non-infectious comorbidities in HIV. http://www.europeanaidscinical-society.org/guidelinespdf/2_Non_Infectious_Co_Morbidities_in_HIV.pdf. Accessed March 30, 2010.
122. National Osteoporosis Foundation. The recommendations and algorithms of the National US Osteoporosis Foundation. <http://www.nof.org>. Accessed May 28, 2010.
123. World Health Organization Collaborating Centre for Metabolic Bone Disease. WHO fracture risk assessment tool. <http://www.shf.ac.uk/FRAX/reference.htm>. Accessed May 28, 2010.
124. Kanis JA, McCloskey EV, Johansson H, Oden A, Ström O, Borgström F. Development and use of FRAX in osteoporosis. *Osteoporos Int*. 2010;21(suppl 2):S407-S413.
125. Mueller NJ, Fux CA, Ledergerber B, et al; Swiss HIV Cohort Study. High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naïve and successfully treated Swiss HIV patients. *AIDS*. 2010;24(8):1127-1134.
126. van Vonderen MG, Lips P, van Agtmael MA, et al. First line zidovudine/lamivudine/lopinavir/ritonavir leads to greater bone loss compared to nevirapine/lopinavir/ritonavir. *AIDS*. 2009;23(11):1367-1376.
127. Brown TT, McCormsey GA. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. *Antivir Ther*. 2010;15(3):425-429.
128. Law MG, Friis-Møller N, El-Sadr WM, et al; D:A:D Study Group. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med*. 2006;7(4):218-230.
129. Kredt T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. *Cochrane Database Syst Rev*. 2009;(3):CD007268.
130. Steigbigel RT, Cooper DA, Kumar PN, et al; BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):339-354.
131. Wittkop L, Breilh D, Da Silva D, et al; ANRS CO3 Aquitaine Cohort. Virological and immunological response in HIV-1-infected patients with multiple treatment failures receiving raltegravir and optimized background therapy, ANRS CO3 Aquitaine Cohort. *J Antimicrob Chemother*. 2009;63(6):1251-1255.
132. Yazdanpanah Y, Fagard C, Descamps D, et al; ANRS 139 TRIO Trial Group. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV. *Clin Infect Dis*. 2009;49(9):1441-1449.
133. Katlama C, Haubrich R, Lalezari J, et al; DUET-1, DUET-2 study groups. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS*. 2009;23(17):2289-2300.
134. Landman R, Capitant C, Descamps D, et al; ANRS 127 Study Group. Efficacy and safety of ritonavir-boosted dual protease inhibitor therapy in antiretroviral-naïve HIV-1-infected patients: the 2IP ANRS 127 study. *J Antimicrob Chemother*. 2009;64(1):118-125.
135. von Wyl V, Yerly S, Böni J, et al; Swiss HIV Cohort Study. Factors associated with the emergence of K65R in patients with HIV-1 infection treated with combination antiretroviral therapy containing tenofovir. *Clin Infect Dis*. 2008;46(8):1299-1309.
136. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS*. 2010;24(2):223-230.
137. Gutmann C, Opravil M, Yerly S, et al. Low-nadir CD4 count predicts failure of monotherapy maintenance with ritonavir-boosted lopinavir: results after premature termination of a randomized study due to unexpectedly high failure rate in the monotherapy arm. In: *16th Conference on Retroviruses and Opportunistic Infections*. Montreal, Canada: CROI; 2009. Abstract 578.
138. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monootherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS*. 2009;23(3):279-291.
139. Soriano V, Puoti M, Garcia-Gascó P, et al. Antiretroviral drugs and liver injury. *AIDS*. 2008;22(1):1-13.
140. Eron JJ, Young B, Cooper DA, et al; SWITCHMRK 1 and 2 investigators. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet*. 2010;375(9712):396-407.
141. De Castro N, Braun J, Charreau I, et al; EASIER ANRS 138 study group. Switch from enfuvirtide to raltegravir in virologically suppressed multidrug-resistant HIV-1-infected patients: a randomized open-label trial. *Clin Infect Dis*. 2009;49(8):1259-1267.
142. Scherrer AU, von Wyl V, Fux CA, et al; Swiss HIV Cohort Study. Implementation of raltegravir in routine clinical practice: selection criteria for choosing this drug, virologic response rates, and characteristics of failures. *J Acquir Immune Defic Syndr*. 2010;53(4):464-471.
143. Cahn P, Fourie J, Grinsztejn B, et al. Efficacy and safety at 48 weeks of once-daily vs twice-daily DRV/r in treatment-experienced HIV-1+ patients with no DRV resistance-associated mutations: the ODIN Trial. In: *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA: CROI; 2010. Abstract 57.
144. Gatell J, Salmon-Ceron D, Lazzarin A, et al; SWAN Study Group. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (A1424-097) 48-week results. *Clin Infect Dis*. 2007;44(11):1484-1492.
145. McIntyre JA, Martinson N, Gray GE. Single dose nevirapine combined with a short course of Combivir for prevention of mother to child transmission of HIV-1 can significantly decrease the subsequent development of maternal and infant resistant virus. *Antivir Ther*. 2005;10:54.