Treatment for Adult HIV Infection

2006 Recommendations of the International AIDS Society–USA Panel

Scott M. Hammer, MD
Michael S. Saag, MD
Mauro Schechter, MD, PhD
Julio S. G. Montaner, MD
Robert T. Schooley, MD
Donna M. Jacobsen, BS
Melanie A. Thompson, MD
Charles C. J. Carpenter, MD
Margaret A. Fischl, MD
Brian G. Gazzard, MA, MD
Jose M. Gatell, MD, PhD
Martin S. Hirsch, MD
David A. Katzenstein, MD
Douglas D. Richman, MD
Stefano Vella, MD
Patrick G. Yeni, MD
Paul A. Volberding, MD

Context Guidelines for antiretroviral therapy are important for clinicians worldwide given the complexity of the field and the varied clinical situations in which these agents are used. The International AIDS Society–USA panel has updated its recommendations as warranted by new developments in the field.

Objective To provide physicians and other human immunodeficiency virus (HIV) clinicians with current recommendations for the use of antiretroviral therapy in HIV-infected adults in circumstances for which there is relatively unrestricted access to drugs and monitoring tools. The recommendations are centered on 4 key issues: when to start antiretroviral therapy; what to start; when to change; and what to change. Antiretroviral therapy in special circumstances is also described.

Data Sources and Study Selection A 16-member noncompensated panel was appointed, based on expertise in HIV research and patient care internationally. Data published or presented at selected scientific conferences from mid 2004 through May 2006 were identified and reviewed by all members of the panel.

Data Extraction and Synthesis Data that might change previous guidelines were identified and reviewed. New guidelines were drafted by a writing committee and reviewed by the entire panel.

Conclusions Antiretroviral therapy in adults continues to evolve rapidly, making delivery of state-of-the-art care challenging. Initiation of therapy continues to be recommended in all symptomatic persons and in asymptomatic persons after the CD4 cell count falls below 350/μL and before it declines to 200/μL. A nonnucleoside reverse transcriptase inhibitor or a protease inhibitor boosted with low-dose ritonavir each combined with 2 nucleoside (or nucleotide) reverse transcriptase inhibitors is recommended with choice being based on the individual patient profile. Therapy should be changed when toxicity or intolerance mandate it or when treatment failure is documented. The virologic target for patients with treatment failure is now a plasma HIV-1 RNA level below 50 copies/mL. Adherence to antiretroviral therapy in the short-term and the long-term is crucial for treatment success and must be continually reinforced.

JAMA. 2006;296:827-843 www.jama.com

THE YEAR 2006 MARKS THE 25TH anniversary of the initial clinical descriptions of what would be later termed the *acquired immunodeficiency syndrome (AIDS)*.[1,2] AIDS has grown to pandemic proportions resulting in 25 million deaths and 40 million persons living with human immunodeficiency virus (HIV) worldwide by the end of 2005.[3] This year is also the 10th anniversary of what has been commonly termed the *HAART (highly active antiretroviral therapy) era*, a decade that began with the introduction of potent 3-drug combination regimens and resulted in substantial reductions in HIV-related morbidity and mortality.[4-7]

Clinical advances have been supported by increased understanding of virologic and immunologic markers of disease stage, viral transmission, and the evolution of viral resistance to antiretroviral drugs. These advances coincided with major breakthroughs in the understanding of disease pathogenesis, the introduction of viral load monitoring, and the clinical application of drug resistance testing.[8-11] Debate continues over the optimal time for initia-

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Author Affiliations: are listed at the end of this article.
Corresponding Author: Scott M. Hammer, MD, Columbia University College of Physicians and Surgeons, 630 W 168th St Box 82, New York, NY, 10032 (smh48@columbia.edu).

Box. Strength of Recommendation and Quality of Evidence Rating Scale

Strength of Recommendation

A: Strong evidence to support the recommendation

B: Moderate evidence to support the recommendation

C: Insufficient evidence to support the recommendation

Quality of Evidence*

Ia, Ib: Evidence from 1 or more published randomized, controlled clinical trials

IIa, IIb: Evidence from nonrandomized clinical trials; cohort or case-control studies

III: Recommendation based on the panel's analysis of the accumulated available evidence

*"a" Indicates published in the peer-reviewed literature and "b" indicates presented in abstract form at peer-reviewed scientific meetings.

tion of antiretroviral therapy, driven primarily by the range of metabolic complications and other toxicities associated with treatment regimens, the consequences of suboptimal adherence, and drug class cross-resistance.

The International AIDS Society–USA panel has published its antiretroviral therapy guidelines 7 times since 1996, a period that coincides with the rapid evolution in practice brought on by the HAART era. The rationale for issuing revised guidelines in 2006 is based on several developments: (1) continued refinement of the recommended initial treatment regimen with a focus on the nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) components of nonnucleoside reverse transcriptase inhibitor (NNRTI)– and protease inhibitor (PI)–based regimens; (2) the US Food and Drug Administration (FDA) approvals of tipranavir and darunavir, which provide new options for management of treatment-experienced patients; (3) the redefinition of the goal of regimens for highly treatment-experienced patients to achieve plasma human immunodeficiency virus 1 (HIV-1) RNA levels below assay detection limits; (4) the availability of a triple-drug combination formulated in 1 pill to be given once daily; and (5) new information on drug-sparing therapeutic strategies, such as supervised treatment interruptions and ritonavir-boosted PI monotherapy.

The guidelines are internationally based and designed for caregivers who practice in relatively resource-unconstrained environments with regard to the availability of drugs and monitoring tools. However, the principles of therapy outlined in these guidelines are pertinent to antiretroviral rollout initiatives in resource-limited settings in that key to the success of such programs are use of potent combinations of drugs designed to fully suppress virus replication, excellent adherence, and avoidance of toxicity.[12] As drugs and diagnostic tools become more affordable and widely available, the principles outlined herein can help guide national programs in the developing world.

The panel was originally convened by the International AIDS Society–USA in 1995 to prepare evidence-based guidelines for the treatment of adult HIV infection. Its last report was in 2004.[13] Physician members were selected based on their expertise in HIV basic science, clinical research, and patient care. Panel members are not compensated; random rotations have been initiated such that one quarter to one third (4 or 5 members) now rotate off the panel after each new report.

The full panel reconvened in October 2005 to consider new data relevant to the current guidelines and met in person or by conference call regularly thereafter. Data published or presented at selected scientific conferences from mid 2004 through May 2006 were reviewed by the panel members. A MEDLINE search was conducted to identify published trials with antiretroviral agents used during that time frame; of 749 citations identified, 181 were considered potentially relevant. In addition, published or presented data from mid 2004 on were requested from all manufacturers of antiretroviral products that were FDA approved or available via expanded access as of January 1, 2006. Data were critically reviewed in a systematic fashion. Specific panel members were appointed to modify the rating scale (M.A.T.); conduct the MEDLINE search (P.A.V.); and prepare drafts of each of the manuscript sections based on panel review and discussion of available data (S.M.H., M.S.S., M.S., J.S.G.M., R.T.S.). All drafts and searches were reviewed by the entire panel.

The quality and strength of the evidence were rated according to a scale adapted from those used by other organizations (eg, American Heart Association,[14] American Association for the Study of Liver Diseases,[15] National Institutes of Health,[16] and Infectious Diseases Society of America[17] (BOX).

This report focuses on 4 issues pertinent to antiretroviral management of adult HIV disease in the setting of routine clinical care: when to start therapy, what drugs to use in the initial regimen, when to change a regimen, and what to change. This report also includes clinical management recommendations for selected special patient situations for which unique considerations are required. New evidence that has led to changes in the guidelines since the last report is described. In areas in which the guidelines have not changed, supportive evidence can be found in the previous report.[13]

When to Start Antiretroviral Therapy

Antiretroviral therapy is recommended for all patients with symptomatic HIV disease (AIa; TABLE 1).[13] For patients without symptoms, therapy should be initiated at some point after the CD4 cell count declines below

350/μL but before it reaches 200/μL (AIIa). No new evidence has emerged to define the optimal CD4 cell count that provides a treatment-related survival advantage, and based on the inherent difficulty with designing and executing such studies, it is unlikely that a randomized, controlled trial will be conducted to answer this question. Rather, recommendations rely on well-conducted cohort studies.[18] Data from one observational study showed a benefit to starting therapy when CD4 cell counts were higher than 350 cells/μL compared with starting at an unspecified later time, but these data do not resolve the questions of the precise CD4 cell count at which to start.[19]

Individualization continues to guide the timing of treatment initiation, with consideration of patient readiness, rate of CD4 cell count decline, and plasma HIV-1 RNA level.[13] Newer formulations of antiretroviral drugs and combinations with improved tolerance and convenience may mitigate previous reluctance to begin therapy early.

The debate about aggressive antiretroviral treatment of primary (acute) HIV infection continues. Recent reports of substantial depletion of CC chemokine receptor 5 (CCR5)–expressing CD4 cells in gut-associated lymphoid tissue in the setting of primary infection, which may be slow or refractory to reconstitution with antiretroviral therapy, represent advances in the understanding of HIV pathogenesis that confirm earlier studies in the simian immunodeficiency virus—rhesus macaque system.[20-23] It remains to be determined what the implications are for the timing of therapy in established HIV infection.

Table 1. Recommendations for Initiating Antiretroviral Therapy in Treatment-Naive Adults With Chronic HIV Infection*

Measure	Recommendation (Rating)†
Symptomatic HIV disease	Antiretroviral therapy recommended (AIa)
Asymptomatic HIV disease	
CD4 cell count ≤200/μL	Antiretroviral therapy recommended (AIIa)
CD4 cell count <350/μL but >200/μL	Antiretroviral therapy should be considered and decision individualized (see subsection "When to Start" [AIIa])‡
CD4 cell count ≥350/μL but ≤500/μL	Antiretroviral therapy generally not recommended (BIIa)§
CD4 cell count >500/μL	Antiretroviral therapy generally not recommended (BIIa)

Abbreviation: HIV, human immunodeficiency virus.
*In nonpregnant adults only. For all individuals regardless of whether they are receiving treatment, intensive counseling to prevent secondary transmission is indicated. Adapted from Yeni et al.[13]
†See Box for definitions of ratings.
‡The closer the CD4 cell count is to 200/μL, the stronger the recommendation, particularly if the plasma viral load is high (>100 000 HIV-1 RNA copies/mL) or if the CD4 cell count is declining rapidly (>100/μL per year).
§Consider treatment for patients with high plasma viral load (>100 000 HIV-1 RNA copies/mL) or with rapid decline of CD4 cell count.

Choice of Initial Regimen

Recent Data. Since the last edition of these guidelines, clinical trial and cohort studies have led to refinements in the choice of initial regimen. The recommended initial regimen remains a combination of 2 nRTIs with either an NNRTI or a PI boosted with low-dose ritonavir. Given the high degree of comparability of the recommended components of these regimens in treatment-naive persons with drug-susceptible virus, the choice of drug centers on acceptability; predicted tolerance; pill burden; comorbid conditions; short-term, mid-term, and long-term adverse event profiles; and successful alternatives should the initial regimen fail and drug resistance emerge. The successful outcomes of several "switch studies" suggest that the initial choice of regimen does not preclude safely changing drugs once viral suppression is achieved.

There are no data to establish that either an NNRTI- or a PI/ritonavir-based regimen is superior in efficacy at any stage of disease. Although some providers prefer a ritonavir-boosted PI over an NNRTI in very advanced disease with high viral loads because of the higher genetic barrier to resistance and slower rate of mutation selection seen with PIs, data to support PI- over NNRTI-based regimens are not yet reported. They perform equally well in settings with low CD4 cell counts and high plasma HIV RNA levels.

Specific considerations in selecting an initial regimen include results of baseline genotypic drug resistance testing; viral hepatitis coinfection status; presence of lipid abnormalities, diabetes mellitus, cardiac, hepatic, or renal dysfunction; reproductive status and use of contraception; and concomitant medications (see the "Special Populations" subsection).

NNRTI-Based Regimens. Data continue to accrue confirming the efficacy and ease of NNRTI-based regimens. Efavirenz plus 2 nRTIs has become a standard-of-care comparator in clinical trials. Efavirenz use requires adequate contraception in women of child-bearing potential given its teratogenic risk in the first trimester. Efavirenz is available in a fixed-dose formulation with tenofovir and emtricitabine, which allows patients to take only 1 pill a day.

Nevirapine has virologic activity similar to efavirenz and is safe for the fetus in all stages of pregnancy if appropriate for the mother. There is a risk of potentially fatal hepatotoxicity in women with CD4 cell counts higher than 250/μL and in men with counts higher than 400/μL. Data from Thailand,[24] where the drug was well tolerated in the patients studied, have raised the question about the true risk to women and whether it applies to all populations. It is not known whether switching from efavirenz to nevirapine when the CD4 cell count has risen above these thresholds while receiving treatment is associated with the same risk as starting nevirapine de novo in a treatment-naive woman or man with CD4 cell counts higher than 250 or 400 cells/μL, respectively.

Since the last Guidelines publication, data confirm that 4 drugs are generally no better than 3 drugs when con-

sidering treatment with currently available nRTIs and PIs in treatment-naive patients not infected with drug-resistant virus.[25] In the final analysis of AIDS Clinical Trials Group (ACTG) A5095, which had previously shown that the zidovudine, lamivudine, and abacavir regimen was inferior to efavirenz plus 2 nRTIs,[26] efavirenz plus zidovudine and lamivudine performed comparably to efavirenz plus zidovudine, lamivudine, and abacavir with 80% and 86% rates of virologic suppression to less than 50 HIV-1 RNA copies/mL of plasma at 48 weeks, respectively.[27]

PI-Based Regimens. Ritonavir-boosted PIs remain a standard-of-care option for initial treatment.[13]

The largest cumulative data set exists for ritonavir-boosted lopinavir, which now is available in a formulation that does not require refrigeration. This is especially important for the developing world. To the developed world, it offers convenience and lower pill burden. Since our last report, ritonavir-boosted lopinavir has been approved for once daily dosing in treatment-naive patients in the United States. Approvals in other countries are pending. The incidence of diarrhea is greater with 800 mg of lopinavir with 200 mg of ritonavir given once a day than with 400 mg of lopinavir with 100 mg of ritonavir twice a day. Lipid elevations appear comparable. The single dosage of ritonavir-boosted lopinavir is not approved for treatment-experienced persons or for children.

Direct comparative trials of ritonavir-boosted fosamprenavir or atazanavir vs lopinavir in treatment-naive patients have not been formally reported; however, results of a study of the latter comparison (the KLEAN trial) are expected to be released in August 2006. Ritonavir-boosted atazanavir has the potential advantage of causing less hyperlipidemia than other ritonavir-boosted PIs.[28] Its major drug-specific adverse effect is hyperbilirubinemia, which is more frequent in persons with the uridine 5′diphospho-glucuronosyl transferase (UGT) UGT1A1-28 genotype or the CC genotype of the 3435C→T polymorphism in the multidrug resistance (*MDR1*) gene.[29-31] The latter is associated with higher atazanavir levels and thus a greater risk of hyperbilirubinemia. These genotypic associations, along with the HLA-B-5701 genotype associated with abacavir hypersensitivity, may ultimately lead to a greater degree of individualization of therapy with routine genotypic profiling of patients in the future. However, it is premature to recommend this form of patient screening. With atazanavir in particular, the indirect hyperbilirubinemia is generally asymptomatic and unassociated with liver enzyme elevations. Knowledge of an increased risk of hyperbilirubinemia would not necessarily preclude its use.

Resistance patterns at the time of virologic failure among participants in the Bristol-Myers Squibb AI424-089 trial[32] support the use of ritonavir-boosted atazanavir over atazanavir alone when choosing this agent as part of an initial regimen. In this study, 200 treatment-naive participants were randomized to receive atazanavir or atazanavir plus ritonavir each in combination with extended-release stavudine and lamivudine. In the intent-to-treat analysis, at 48 weeks, HIV-1 RNA suppression to levels less than 50 copies/mL was comparable: 70% and 75%, respectively. Of the 10 virologic failures in the atazanavir-alone group, PI mutations were seen in 3 and nRTI mutations in 10 participants. Of the 3 virologic failures in the group receiving atazanavir plus ritonavir, no PI mutations and 1 nRTI mutation were seen. Hyperbilirubinemia and lipid elevations were greater in the group receiving atazanavir plus ritonavir.

In the MaxCmin2 trial,[33] 400 mg of lopinavir and 100 mg of ritonavir twice daily plus 2 nRTIs was compared with the soft-gel formulation of 1000 mg of saquinavir plus 100 mg of ritonavir twice daily plus 2 nRTIs in treatment-naive participants. At 48 weeks, the virologic failure rate was higher in the saquinavir-plus-ritonavir group. This difference may have occurred because patients had less tolerance for the saquinavir-based combination than those taking the lopinavir-based combination. A trial with the saquinavir hard-gel formulation showed good virologic efficacy.[34]

Dual nRTI Components. Nonnucleoside reverse transcriptase inhibitors or PIs typically are given with 2 nRTIs in combinations that have advantages with respect to side effect profiles and availability in fixed-dose combinations; virologic potencies appear comparable. Since the last edition of the guidelines, data continue to support use of lamivudine or emtricitabine (with these drugs considered interchangeable) as one of the dual nRTI components because each of these thiacytidine compounds is well-tolerated and potent. Lamivudine is available in fixed-dose combinations with either zidovudine or abacavir and emtricitabine has been coformulated with tenofovir disoproxil fumarate. As dual nRTI components, zidovudine and lamivudine, abacavir and lamivudine, and tenofovir and emtricitabine all produce 1.5 to 2.0 $\log_{10}$ copies/mL reductions in plasma HIV-1 RNA levels and early virologic failure usually selects for the M184V substitution associated with resistance to lamivudine or emtricitabine. Thus, assuming the presence of fully drug-susceptible virus, the choice of the dual nRTI component relates to the toxicity profiles and predicted tolerance of zidovudine, abacavir, or tenofovir. Differentiating adverse effects include headache, nausea, anemia, and lipoatrophy for zidovudine; hypersensitivity reaction with abacavir; and renal dysfunction in patients with baseline renal compromise with tenofovir.[35] As a fixed-dose combination, zidovudine and lamivudine is given twice daily; abacavir and lamivudine and tenofovir and emtricitabine are given once daily.

In a recent randomized controlled trial, zidovudine plus lamivudine was compared with tenofovir plus emtricitabine, each in combination with efavirenz in 517 treatment-naive participants.[35] Tenofovir and emtricitabine with efavirenz resulted in 80% plasma viral suppression below 50 HIV-1 RNA copies/mL at 48 weeks com-

pared with 70% for zidovudine and lamivudine. The former was also superior in CD4 cell count responses and adverse events. There were more discontinuations in the zidovudine and lamivudine group. Better tolerance of tenofovir and emtricitabine, rather than differences in intrinsic antiretroviral activity, may explain these results.

Important data for the field concerning an nRTI-sparing strategy are pending from the analysis of ACTG A5142, which is comparing lopinavir and ritonavir plus 2 nRTIs; efavirenz plus 2 nRTIs; and lopinavir and ritonavir plus efavirenz.

Recommendations. Either of 2 basic 3-drug regimens continues to be recommended for initial therapy: NNRTI-based or PI ritonavir-boosted–based combinations. Of the NNRTIs, efavirenz is recommended due to its consistent efficacy demonstrated in numerous randomized trials and its toxicity profile (AIa).[35-37] Efavirenz is not recommended for women in the first trimester of pregnancy (AIIa). Nevirapine is recommended as the NNRTI component for women in whom pregnancy may occur on treatment or who are pregnant and have fewer than 250 CD4 cells/μL (AIIa). Nevirapine is also recommended as an alternative NNRTI in men or women in whom the central nervous system toxicity of efavirenz is not tolerated or does not abate within 2 to 3 weeks of starting treatment.[38] The drug should be avoided as initial therapy in women with CD4 cell counts higher than 250/μL and in men with CD4 cell counts higher than 400/μL (AII).

Of the ritonavir-boosted PIs, recommended components are lopinavir (AIa), atazanavir (BIII), fosamprenavir (BIII), or saquinavir (BIII). More data exist for lopinavir and ritonavir but the hyperlipidemia and other metabolic consequences of therapy also support use of atazanavir and ritonavir. Induction of hyperlipidemia with atazanavir and ritonavir is lower than lopinavir and ritonavir; the most frequent agent-specific adverse effect of atazanavir is asymptomatic hyperbilirubinemia. Data comparing lopinavir and ritonavir and atazanavir vs ritonavir in treatment-naive persons are not yet available and will be important. The efficacy of the soft-gel formulation of saquinavir and ritonavir was inferior to lopinavir and ritonavir[33] but this was probably due to differences in tolerability and the hard-gel formulation has good virologic efficacy. Data on fosamprenavir and ritonavir support its use in initial regimens. The choice is dependent on provider and patient preference.

Recommended nRTI components in the initial regimen are tenofovir and emtricitabine (AIa), zidovudine and lamivudine (AIa), or abacavir and lamivudine (AIa). Tenofovir is well tolerated but should be used with caution, or avoided, in patients with preexisting renal insufficiency (AIa).

There are almost 20 years of accrued data for zidovudine but, as a thymidine analogue, it produces adverse gastrointestinal tract, central nervous system, and mitochondrial effects more frequently than tenofovir or abacavir. Abacavir, in combination with lamivudine, has comparable antiretroviral activity with the other dual nRTI components listed. However, abacavir-containing regimens carry a 5% to 8% risk of discontinuation due to a hypersensitivity reaction. The risk of abacavir hypersensitivity has been associated with the HLA-B-5701 genotype in some populations and genotypic profiling of patients for whom abacavir therapy is being considered.[39,40] Furthermore, abacavir retains activity against viruses with the M184V substitution that occurs commonly with regimens containing lamivudine or emtricitabine, making the drug useful in constructing regimens in which these nRTIs have failed. TABLE 2 presents the considerations for each nRTI backbone.

Other nRTIs can be combined for initial regimens if none of the recommended combinations can be used. However, certain nRTI components should not be combined. Zidovudine and stavudine should not be used because of antagonism (AIa). Stavudine and didanosine should not be used (AIa) because of overlapping toxic effects, and tenofovir and didanosine should not be used in treatment-naive patients with wild type virus (AIa) because of dampened CD4 cell responses and toxic effects.[49-52] Its cautious use in treatment-experienced patients can be considered, however, when treatment options are more limited. Also, abacavir and tenofovir should not be used as the dual nRTI component of an initial regimen because of genetic fragility (eg, K65R substitution emergence and impact).

Triple nRTI regimens are inferior to NNRTI- or ritonavir-boosted PI–based regimens and should only be used in highly selected circumstances, such as high risk of toxic effects, drug-drug interactions, or patient nonadherence to an NNRTI or PI and ritonavir component. Of the triple nRTI regimens, the largest experience is with zidovudine, lamivudine, and abacavir but it is inferior to efavirenz-based regimens.[26] Zidovudine, lamivudine, and tenofovir is currently under investigation in the Development of Antiretroviral Therapy in Africa trial[53] and quadruple nRTI regimens (eg, zidovudine, lamivudine, abacavir, and tenofovir) remain experimental.[54]

Patient Monitoring

Considerations. Recommendations for the initial workup of newly diagnosed HIV-infected persons have been published recently.[7,55] Baseline and periodic CD4 cell counts and plasma HIV-1 RNA levels, and in selected settings, baseline drug resistance genotypic testing (see below) are indicated to guide decision making, as is evaluation for comorbid conditions that may influence the timing and choice of initial therapy (presence of hepatitis B or C virus [HBV or HCV] infection, diabetes mellitus, hyperlipidemia, coronary artery disease, renal disease, etc).

Monitoring Treatment Response. The aim of antiretroviral therapy remains the maintenance of the plasma HIV-1 RNA level below the limits of detection of the most sensitive assays commercially available (ie, less than 50 copies/mL).[13] Effective regimens and high

levels of adherence result in a decrease of at least 1.0 $\log_{10}$ copies/mL or 90% per month and suppression of plasma HIV-1 RNA level to below 50 copies/mL will generally be achieved by 16 to 24 weeks, depending on pretreatment level.[56] After 48 weeks, measures of HIV-1 RNA should be obtained at regular intervals (eg, every 3 or 4 monthly) to confirm that the plasma HIV-1 RNA level remains below the limits of detection.[57,58] A confirmed rebound in plasma HIV-1 RNA level after achieving an undetectable level should prompt a careful evaluation of the patient's adherence to the treatment regimen. Although isolated low-level rebounds (range, 50-500 copies/mL) in HIV-1 RNA level are often of no clinical consequence, consecutive rebounds in plasma HIV-1 RNA higher than 500 copies/mL can be associated with the development of drug resistance mutations and virologic failure.[59]

Table 2. Recommended Components of Initial Antiretroviral Therapy and Considerations for Choosing the Regimen

Component	Considerations for Choice	Major Toxic Effects and Cautions	Resistance Considerations
Nucleoside (or nucleotide) reverse transcriptase inhibitors			
Tenofovir*/emtricitabine†	Well tolerated Efficacy >zidovudine/lamivudine[35] or stavudine/lamivudine[41] Available as a fixed-dose Spares thymidine analogues 1/d	Baseline renal function should be evaluated before initiating tenofovir Use with caution or avoid in patients with renal dysfunction	M184V, K65R
Zidovudine/lamivudine‡	Most extensive clinical trial data set and phase 4 experience supporting use Standard-of-care comparator in many trials, 2/d Available as a fixed-dose	Headache, nausea Anemia Lipoatrophy	M184V, thymidine analogue-associated mutations
Abacavir/lamivudine‡	Supportive clinical trial data Spares thymidine analogues Available as a fixed-dose 1/d	Hypersensitivity syndrome in 5% to 8% of persons (greater risk in person with the HLA-B5701 genotype)	M184V, K65R
Nonnucleoside reverse transcriptase inhibitors			
Efavirenz	Efficacy proven in controlled trials Standard-of-care comparator in many trials Available as a fixed dose	Central nervous system toxic effects may be limiting Teratogenic in first trimester of pregnancy	Single-step high-level resistance occurs with treatment failure with cross-resistance to nevirapine
Nevirapine	Efficacy proved in controlled trials Safe to the fetus	Rash Hepatotoxicity Hypersensitivity syndrome Avoid in women with >250 CD4 cells/μL and men with >400 CD4 cells/μL	Single-step high-level resistance occurs with treatment failure with cross-resistance to efavirenz
Ritonavir-boosted protease inhibitors			
Ritonavir-boosted lopinavir	Substantial clinical trial data set and phase 4 experience supporting efficacy Heat-stable formulation available 1 or 2/d for treatment naive; 2/d, for treatment experienced	Gastrointestinal adverse effects Hyperlipidemia Lipodystrophy Insulin resistance	Protease inhibitor mutations are rare in treatment failure if virus is fully susceptible at baseline
Ritonavir-boosted atazanavir§	Decreased potential for hyperlipidemia than with other protease inhibitors 1/d	Hyperbilirubinemia (UGT1A1-28 alleles and T3435C polymorphism in *MDR1* gene) Avoid concomitant antacid use (separate dosing times) Do not use concomitant proton pump inhibitors	Limited data on resistance mutations in previously antiretroviral-naive patients
Ritonavir-boosted fosamprenavir§	No food restrictions	Rash	Limited data on resistance mutations in previously antiretroviral-naive patients
Ritonavir-boosted saquinavir§	Lower lipid effects(?) Soft-gel formulation is less effective than ritonavir-lopinavir[33]	Gastrointestinal toxic effects with soft-gel formulation; incidence diminished with hard-gel formulation	Limited data on resistance mutations in previously antiretroviral-naive patients

*Recent guidelines recommend a baseline urinalysis and estimation of creatinine clearance or glomerular filtration rate rather than serum creatinine level alone for assessment of renal function.[17] Patients receiving tenofovir should be observed for the development of renal dysfunction because this toxic effect occurs in a small proportion of treated patients but may require intervention.[42-48] To date, the prevalence and predictors for this toxic effect have not been fully established, so vigilance in all patients receiving tenofovir is warranted.
†Or lamivudine.
‡Or emtricitabine.
§Direct comparisons between this drug and ritonavir-boosted lopinavir are under way.

Resistance Testing. Genotypic and phenotypic assays are widely used to evaluate HIV resistance to antiretroviral drugs.[60] In the setting of treatment experience, resistance testing should be performed while the patient is taking the failing regimen. Resistance assays may also be of value in selecting the initial treatment regimen, because transmission of drug-resistant HIV strains leading to suboptimal virologic responses has been documented and there is evidence of increasing rates of drug resistance among newly diagnosed patients both in Europe and the United States.[61] Early virologic failure in patients receiving combination antiretroviral therapy has been shown to be often associated with resistance to a single component of a multidrug regimen.[62,63]

Results for genotypic assays can be available in 1 to 2 weeks, whereas results for phenotypic assays can take 3 to 4 weeks; however, interpretation may be complex, requiring precise knowledge of the mutations associated with decreased susceptibility to each antiretroviral drug, the interactions among these mutations, and their potential to confer cross-resistance.[64] Expert advice should be sought whenever possible to interpret genotypic results.

Phenotypic assays quantify the ability of the virus to grow in varying concentrations of specific antiretroviral drugs. Automated recombinant virus phenotypic assays are commercially available; however, the test usually requires weeks for turnaround and is more expensive than genotypic testing.

Cost, differing interpretations of resistance testing, and insensitivity for detection of minor viral species are limitations of genotypic and phenotypic tests. Both tests identify only the predominant circulating virus in plasma (dependent on the selective pressure exerted by the patient's current regimen).

Therapeutic Drug Monitoring. Therapeutic drug monitoring (TDM) is of potential interest because of interpatient variability in drug exposure and the established relationships among drug exposure, therapeutic effect, and toxic effects. Protease inhibitors and NNRTIs are candidates for TDM because serum concentration–response relationships are relatively well characterized. Because the active moieties of nRTIs are intracellular triphosphate, or diphosphate in the case of tenofovir, forms of the drugs, measuring serum levels of these agents is less helpful.

Expert advice is recommended when using TDM. The role of TDM in clinical practice remains controversial largely due to the lack of prospective studies demonstrating that TDM improves clinical outcome. In addition, one has to be certain that the laboratory used can reliably measure antiretroviral drug concentrations under rigorous quality control standards.

Fitness Testing. Antiretroviral resistance mutations may affect the capacity of HIV to replicate in vitro as measured by replication competence, which is considered a reflection of in vivo viral fitness. A virus with a lower replicative capacity in vitro may be associated with less virulence in vivo as measured by the rate of CD4 cell loss or clinical disease progression, but this has not been established in prospective clinical trials. Some would continue to prescribe a drug whose signature resistance mutations are associated with compromised replicative capacity if the agent is well tolerated and CD4 cell level and clinical status are stable, even in the face of established resistance to that drug.

Recommendations. Once antiretroviral therapy is initiated, plasma HIV-1 RNA level should be checked relatively frequently (eg, every 4-8 weeks; AIIa) until it reaches levels below the limits of detection of the assay and regularly thereafter (eg, 3 times per year to 4 times per year [BIII]).[65] CD4 cell count generally should be monitored in tandem with HIV-1 RNA level.

Genotypic testing for HIV resistance is preferred over phenotypic testing in most settings because it is faster, readily available, and less expensive; phenotypic testing may be more useful for patients with virologic failure following 2 or more regimens. Baseline resistance testing is recommended if the prevalence of transmitted HIV drug resistance is greater than 5% (BIII) and should be considered if the prevalence is unknown, but antiretroviral penetration in the population is thought to be high enough that transmission of drug resistance is likely (BIII). Thus, resistance testing has become a routine part of the baseline evaluation of patients with established infection in many settings.[7] Resistance testing is recommended in the setting of virologic failure (AIa) and ideally should be performed when the patient is taking the failing regimen, which maximizes selective pressure on the virus thus increasing the likelihood that resistance testing will detect the mutations that the patient harbors. Resistance testing should also be considered after a new regimen is introduced if the HIV-1 RNA trajectory is not optimal (AII). Drug-resistance testing should not be performed if the plasma HIV-1 RNA level is below 500 to 1000 copies/mL because the assay does not perform reliably at that level.

Therapeutic drug monitoring for NNRTIs and PIs has entered clinical practice in a number of countries (eg, Western Europe and Canada) but in others remains a research tool and is not recommended as a part of routine care (CIII). Monitoring of serum nRTI concentrations is not recommended in clinical practice (CIII). Replication-capacity assays are also not recommended as part of routine care, although, as noted, this in vitro viral characteristic is already being reported by at least 1 commercial drug-resistance testing company (CIII).

When to Change and What to Change

Recent Data. Despite availability of regimens that are potent, well tolerated, convenient, and relatively easy to take, many patients still require a change in regimen, often related to treatment-related toxic effects, intolerance, inconvenience, or failure. Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels

below 50 copies/mL even in highly treatment-experienced patients.[66,67] Similarly, several studies have demonstrated that many treatment-related toxic effects can be avoided, reversed, or at least partially controlled with judicious modifications of antiretroviral regimens.[68,69]

Changing for Reasons of Intolerance, Inconvenience, or Toxic Effects. Intolerance or toxicity frequently occurs within the first several weeks of starting a new regimen. In a previously treatment-naive patient not expected to harbor archived drug resistance mutations, if 1 offending drug can be identified, changing only that drug in an otherwise successful regimen is virologically safe. With some acute toxic effects such as rash, hepatic dysfunction, and febrile systemic reactions, it may be best to stop all antiretroviral drugs.

The principle of switching a single agent for management of toxic effects may apply to late onset effects as well. For instance, atazanavir is less likely to cause increased lipid levels than other PIs,[70] and lipoatrophy is more commonly associated with stavudine than with other nRTIs.[69] Switching from a thymidine analogue to a nonthymidine analogue and from a hyperlipidemia-inducing PI and ritonavir to atazanavir and ritonavir may be a useful clinical strategy.[71]

Changing for Treatment Failure. The benefits of plasma HIV-1 RNA suppression to less than 50 copies/mL on durability of response and prevention of emergence of resistance support using persistent elevations above this cutoff as a definition of virologic failure. Previous guidelines recommended establishing a plasma HIV-1 RNA target of at least 0.5 to 1 $\log_{10}$ HIV-1 RNA copies/mL below baseline for patients with more advanced treatment failure and a high level of multidrug resistance. However, several recent studies evaluating newer antiretroviral agents designed to have activity against multidrug-resistant virus have demonstrated that a high proportion of heavily treatment-experienced patients can achieve HIV-1 RNA levels of less than 50 copies/mL.[66,72,73] When this is not achievable, stability of CD4 cell count and clinical status usually can be maintained for relatively long periods with reductions of HIV-1 RNA to levels at least 0.5 to 1.0 $\log_{10}$ copies/mL below baseline, although cumulative acquisition of new resistance mutations is a consequence of this approach. Isolated episodes of intermittent viremia or transient episodes of plasma HIV-1 RNA levels higher than 50 copies/mL but lower than 500 to 1000 copies/mL do not necessarily predict subsequent virologic failure and should not prompt an immediate change in therapy.[74]

For selecting subsequent therapy, data from recent trials showed no benefit of double-boosted PIs (2 active PIs and low-dose ritonavir) over single-boosted PIs.[66,72] Moreover, pharmacokinetic interactions, tolerance, and long-term adverse effects complicate double-boosted PI therapy.

Drug-Sparing Strategies. *Ritonavir-Boosted PI Monotherapy.* The potency and high genetic barrier to resistance of ritonavir-boosted PIs might make them potentially useful as initial therapy or as part of a simplification strategy. In the OK study, 42 participants were randomly assigned to continue lopinavir and ritonavir plus 2 nRTIs or to begin lopinavir and ritonavir monotherapy following suppression to less than 50 copies/mL on lopinavir and ritonavir plus 2 nRTIs. At 48 weeks, 81% and 95% of the participants in the 2 groups, respectively, maintained HIV-1 RNA levels lower than 50 copies/mL. This was not statistically different because the numbers in the trial were small.[75] In the single-group, pilot ACTG A5201 study[76] of 36 participants, simplification of therapy to atazanavir and ritonavir alone following 6 weeks of induction with atazanavir and ritonavir plus 2 nRTIs resulted in a 91% rate of suppression of plasma HIV-1 RNA to less than 50 copies/mL at 24 weeks. In both of these studies, PI mutations were not detected in the patients in whom monotherapy failed virologically. These data are still preliminary but add to the growing experience with nRTI-sparing strategies and suggest that further studies are warranted.

Treatment Interruptions and Intermittent Therapy. Recent studies have demonstrated no beneficial effect, and sometimes deteriorating clinical outcomes, by using structured (or supervised) treatment interruptions (STIs) as a treatment strategy. Two general approaches have been evaluated: therapy interruption done at predefined intervals of time or interruption based on targeted CD4 cell responses.

The Staccato,[77] Window,[78] Trivacan,[79] and Istituto Superiore di Sanità Pulsed Anti-Retroviral Therapy (PART)[80] studies each looked at variable or fixed intervals of treatment interruptions that lasted from weeks to months. A common theme that emerged is that short intervals of stopping and starting therapy can be associated with relatively high rates of emergence of drug resistance and are generally not advisable. Longer intervals of starting and stopping therapy may not result in significantly more failure, but there is no clear consensus on the safety and value of this approach.

Other studies used CD4 cell count triggers of treatment interruption. The Strategies for Management of Anti-Retroviral Therapy study[81] evaluated routine interruption of therapy when CD4 cell counts reached a threshold of more than 350/μL and reintroduction of therapy when the CD4 cell count decreased to less than 250/μL vs continuous therapy. There was increased progression to a new AIDS-defining event or death, as well as more non-HIV–related serious adverse events among those in the STI group than those in the control group. Similarly, the group whose treatment was interrupted by CD4 cell count in the Trivacan study was discontinued early as a result of an increased incidence of severe morbidity.[78]

Available data from ongoing trials evaluating treatment interruptions at higher CD4 cell counts are difficult to interpret, given their lack of statistical power to compare clinical end points.[77,80,82]

Some studies that used STI as a means to improve immunologic host re-

sponses to HIV through autoimmunization have shown some improvement in the level of HIV-1 viremia in the STI group compared with the control group. In one such study, the effect of the STI was small and several participants developed mutations associated with resistance to the drugs in their discontinued regimens and had difficulty reestablishing control of replication when therapy was reintroduced.[83]

New Drugs. Since the previous guidelines, 2 new drugs have become available for use in treatment-experienced patients (TABLE 3).

Tipranavir. A PI designed to have activity against multi-PI-resistant virus is the combination of 500 mg of tipranavir with 200 mg of ritonavir twice a day. The Randomized Evaluation of Strategic Intervention in Multi-drug Resistant Patients with Tipranavir (RESIST) trials I[84] and II[75,85] evaluated tipranavir in patients in whom PI-, NNRTI-, and nRTI-containing regimens had failed. Patients who had 2 or more mutations associated with high-level tipranavir resistance were not eligible for enrollment. The 2 studies had similar inclusion criteria and were conducted in North America, Europe, Australia, and Latin America. The tipranavir-plus-ritonavir group demonstrated greater reductions in plasma HIV-1 RNA levels and increases in CD4 cell counts than did the comparator PI group when each was combined with optimized background regimens. Of note, in this heavily treatment-experienced population, 33% of the enfuvirtide-naive participants achieved levels of less than 50 copies/mL if enfuvirtide was part of the optimized background regimens.[66] The likelihood of reaching an HIV-1 RNA level lower than 50 copies/mL was highest if more than 2 active drugs were in the regimen, especially if 1 of the drugs was enfuvirtide.

The principal toxic effects of tipranavir are gastrointestinal, with approximately 20% of participants experiencing nausea and 30% diarrhea. Fatal and nonfatal intracranial hemorrhage has recently been reported among patients taking tipranavir. Liver enzyme elevations are not uncommon, particularly in patients with chronic HBV or HCV, or with elevated liver enzymes at initiation of tipranavir-ritonavir therapy. As with other PIs, the presence of a greater number of key mutations leads to stepwise reduction in activity.[88] A 1.8-fold phenotypic change in tipranavir susceptibility is associated with reduced activity of tipranavir-ritonavir-containing regimens in the clinical studies conducted thus far. Pharmacologic interactions between tipranavir and other drugs metabolized by the liver may limit its use for patients taking numerous drugs.

Darunavir. Formerly known as TMC-114, darunavir, is a potent new PI also designed to have activity against multi-PI-resistant virus; it is given at a dose of 600 mg twice a day combined with low-dose ritonavir (100 mg twice a day). Darunavir was evaluated in 2 studies (Performance of TMC-114/r When Evaluated in Treatment-Experienced Patients With PI Resistance[POWER] I and II)[86,87] conducted in the United States, Europe, and South America. Entry criteria were similar to that in the RESIST trials[84,85] except that the existence of baseline genotypic mutations associated with PI resistance was not an exclusion criterion. Heavily treatment-experienced participants (eg, there was a 70- to 80-fold reduction in lopinavir susceptibility) were assigned to receive optimized background regimens combined with either darunavir or a comparator PI. The comparator PI subset performed similarly as it had in the RESIST studies. Plasma HIV-1 RNA level reductions and CD4 cell count increases were significantly greater in the darunavir group. Of note, at 24 weeks more than 60% of enfuvirtide-naive participants who were treated with enfuvirtide achieved undetectable levels.[74] POWER III,[67] an open-label study, provided safety and relative efficacy data for darunavir and ritonavir in heavily treatment-experienced patients.

The principal toxic effects of darunavir are gastrointestinal, 18% of participants experienced nausea and 17% diarrhea. Mutations at positions 32, 33, 47, and 54 on the protease gene are associated with reduced susceptibility to darunavir and a 4- to 10-fold change in phenotypic susceptibility is associated with reduced activity of drug.[89]

Recommendations. The recommendations for when to change and what to change to depend on the reasons for changing and on the availability of active drugs for constructing a potent regimen.

Changing Therapy Because of Toxicity, Intolerance, or Inconvenience. Low-grade and often transient symptoms that typically occur early after initiation of therapy (eg, zidovudine-related headache and nausea; efavirenz-related central nervous system adverse effects) can often be addressed with appropriate patient education and symptomatic medications without stopping the offending drug.

In successfully treated patients who need to modify their regimens because of toxic effects or intolerance and in whom the offending agent can be identified with reasonable certainty, single-drug substitution is generally safe, particularly in previously treatment-naive patients not expected to be harboring archived drug-resistance mutations (AII).

When a toxic effect cannot be confidently attributed to a single drug and is severe enough to require temporary discontinuation of therapy, all drugs in the regimen should be stopped (AII).

For patients taking drugs with substantially different half-lives (eg, NNRTI and nRTIs) and whose reason for changing therapy is inconvenience or adverse effects that do not require immediate action, staggered discontinuation of the drugs should be considered (eg, stopping the NNRTI 5 to 7 days before the nRTIs), in an attempt to avoid the emergence of drug resistance (BIII). Nevertheless, given wide interpatient variability, it is not possible to determine with certainty what is a safe time interval for differential stoppage of antiretrovirals.[90] Once the toxicity resolves, a new regimen can often be introduced.

Symptomatic lactic acidosis is a life-threatening condition that is most often associated with the use of nRTIs,

Table 3. Selected Randomized Studies of Tipranavir and Darunavir

Study	Drug	No. of Patients	Population/Prior Antiretroviral Therapy	End Points: CD4 Cell Count/μL	End Points: Log_{10} Copies of HIV-1 RNA/mL	End Points: % With <50 HIV-1 RNA Copies/mL	End Points: Increase in CD4 Cell Count/μL	Important Safety Results
RESIST 1[84]	Tipranavir	620 Treatment-experienced	Virologic failure of ≥1 nRTI, ≥1 NNRTI, ≥2 PIs; ≥1 major PI mutation but ≤2 mutations at codons 33, 82,84, or 90; median of 15 baseline PI mutations in each group					RESIST 1 and 2 pooled data: AST/ALT, +5% to +7%; triglycerides, +20%; higher overall rate of adverse events in ritonavir-tipranavir groups than comparator
Optimized background + 500 mg/d of tipranavir + 200 mg/d of ritonavir				123	4.81	32.8*	36*	
Optimized background + comparator PI				123	4.84	14.3*	6*	
RESIST 2[85]	Tipranavir	863 Treatment-experienced	Virologic failure of ≥1 nRTI, ≥1 NNRTI, ≥2 PIs; ≥1 major PI mutation but ≤2 mutations at codons 33, 82, 84, or 90; median of 12 prior regimens in each group					
Optimized background + 500 mg of tipranavir + 200 mg of ritonavir 2/d				175	4.78	22.5*	31*	
Optimized background + comparator PI				196	4.77	8.6*	1*	
POWER 1[86]	Darunavir	128 Treatment-experienced	Virologic failure of 3 classes; HIV-1 RNA >1000 copies/mL; median of 8 baseline PI mutations in each group					POWER 1 and 2 pooled data: <adverse events vs comparator PI; similar lipid, hepatic, and cardiac toxicity, <glucose effects, >nausea and insomnia with darunavir; >diarrhea with comparator PI
Optimized background + 600 mg of darunavir and 100 mg of ritonavir 2/d†				204	4.5	53*	124*	
Optimized background + comparator PI				233	4.40	18*	20*	
POWER 2[87]	Darunavir	110 Treatment-experienced	Virologic failure of 3 classes; >1 PI mutation; HIV-1 RNA >1000 copies/mL; median of 8 baseline PI mutations in each group; no NNRTI in optimized background					
Optimized background + 600 mg of darunavir and 100 mg of ritonavir 2/d†				99	4.7	39*	59*	
Optimized background + comparator PI				113	4.60	7*	12*	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HIV, human immunodeficiency virus; LPV, lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside (or nucleotide) reverse transcriptase inhibitor; PI, protease inhibitor.
*Statistically significant difference between groups.
†Other dosages were used in the original study but are not reported herein.

particularly with stavudine.[91] Immediate discontinuation of the antiretroviral regimen is indicated. Following complete recovery, the safest course is to introduce an nRTI-sparing regimen, such as a ritonavir-boosted PI with an NNRTI (BII). However, nRTIs less commonly associated with mitochondrial toxicity, such as lamivudine, emtricitabine, tenofovir, and abacavir, may be safely reintroduced following full recovery from this syndrome if the benefit is thought to outweigh the risk. Close monitoring of symptoms and lactate levels is required if this is attempted (BIII). Of note: routine lactate monitoring in an asymptomatic individual who has not experienced an episode of lactic acidosis is not recommended.

In the case of hyperlipidemia, adjustments in the antiretroviral regimen are recommended as a primary approach if diet and exercise fail to control lipid levels (AI).[68-70] For patients who do not want to change their regimen, the addition of a lipid-lowering agent is an acceptable strategy (AII). If other viable agents with presumptive antiretroviral activity are not available, then it is more appropriate to add specific antilipid therapy (AI). When there are changes in body fat distribution, particularly lipoatrophy, switching the putatively offending antiretroviral agent(s) may halt further progression of the body-shape changes and, in some cases, can lead to some degree of reversal of the abnormality over an extended period (AI).[69] However, selection of the next regimen often poses management challenges because a number of drugs from different classes are associated with lipodystrophy. Given that replacing the drug(s) responsible usually does not completely reverse the abnormality, close monitoring for the first signs of body fat changes and early switching, if options exist, are recommended (AII).[92]

Changing Therapy Because of Treatment Failure. Treatment failure may be defined virologically, immunologically (declining CD4 cell count), or clinically (HIV-related disease progression). Viral rebound should be confirmed to ensure that it is not transient (ie, a blip).

FIRST REGIMEN FAILURE. The fundamental principle for managing any regimen failure, regardless of how many prior regimens the patient has experienced, is to ensure that at least 2, and preferably 3, drugs used in the new regimen are likely to have activity based on integration of resistance test results and history of antiretroviral regimen use. In individuals in whom the first regimen fails and who were likely infected with a drug-susceptible virus, a full assessment of adherence is the first step. Particular attention should be paid to subtle toxic effects, such as low-grade nausea or headache, which may interfere with optimal adherence. If attempts at improving adherence fail and plasma HIV-1 RNA levels are confirmed to be higher than 500 to 1000 copies/mL, resistance testing should be obtained. Full susceptibility to all drugs in the regimen suggests that the patient is not taking the drugs. If drug resistance is detected, the regimen should be altered so that there are at least 2 fully active drugs in the regimen.

MULTIPLE REGIMEN FAILURE. In the setting of 3 or more regimen failures, management challenges increase substantially. Subsequent regimen failures cause further drug resistance that limits the remaining antiretroviral options. A crucial concept when initiating a new regimen after treatment failure is the requirement of preferably 3, but at least 2, fully active agents as determined by resistance test results and prior treatment history (AI). If at least 2 drugs cannot be identified, strong consideration should be given to maintaining the current regimen until new drugs become available, assuming immunologic and clinical stability (AI). Investigational drugs often become available through clinical trials and physicians should be vigilant for drugs in development that may become available. The use of a single-active drug, so-called sequential monotherapy, should be avoided since it usually leads to rapid development of resistance to that drug, further limiting future treatment options (AI). When 2 or more potent drugs are identified, the goal of therapy should be the achievement of HIV-RNA levels below 50 copies/mL, even for highly treatment-experienced patients (AI). If durable undetectable levels of HIV-1 RNA are deemed unachievable, the goal of therapy shifts to maintenance of immunologic integrity and prevention of clinical disease progression with acceptance of incomplete viral suppression (AII).

When choosing the next regimen, maintenance of nRTI agents in the regimen still contributes some antiviral activity, even when formal resistance is detected.[93] In particular, lamivudine or emtricitabine often continues to have significant activity (0.5 to 0.8 $\log_{10}$-copies/mL declines) even when resistance-conferring mutations to these drugs are present (eg, the M184V or L44I substitutions).[94] In contrast, currently available NNRTIs typically have no virologic activity when high-level resistance is demonstrated and should not be continued in the next treatment regimen (AI).

There are no convincing data to support the use of a double-boosted PI and these combinations should be avoided (AI).

The RESIST[66] and POWER[67] studies have helped define the optimal time in which to use enfuvirtide. If several potent drugs other than enfuvirtide are available, it may be best to defer enfuvirtide use until it becomes 1 of 2 available and fully active drugs (AII). However, since the goal of therapy is to achieve plasma HIV-1 RNA levels of less than 50 copies/mL, enfuvirtide often is required to achieve this degree of success among heavily antiretroviral-experienced patients (AI). There are limited and somewhat conflicting data on the potential benefit of maintaining enfuvirtide in the regimen during virologic failure. In these patients, enfuvirtide-resistant virus is frequently present. Although resistance to enfuvirtide may be associated with decreased viral replicative capacity, its re-

moval from the regimen may not lead to significant drops in CD4 cell count.[95] Thus, given its cost and inconvenience, consideration should be given to stopping enfuvirtide in case of virologic failure (BIII); additional data are needed to guide clinicians with this decision.

Discordant Responses. Some patients experience a discordant response, whereby the HIV-1 RNA level is below the limit of detection but the CD4 cell count response is blunted. In such settings, it is prudent to continue the current regimen (AII). Changing or intensifying the regimen has not been shown to have an effect on the CD4 cell count response, except in the case of patients using drugs that are associated with lymphopenia (zidovudine or didanosine; AII). The use of interleukin-2 may cause significant toxic effects and no clinical benefit has yet been documented; thus, it should not be used except in clinical trials (AIII). Other patients may exhibit a different pattern of discordant response, characterized by a sustained CD4 cell count response, despite persistent viremia. Both types of discordant responses, particularly the former, have been associated with rates of progression to AIDS or death that are intermediate between those observed in complete responders and in nonresponders.[96-98]

Treatment Interruptions and Intermittent Therapy. At present, a treatment interruption for successfully treated patients is not recommended outside of clinical trials (AI). Cycles of STI in patients with controlled viremia simply to reduce long-term exposure to the drugs are also not recommended (AII). Similarly, STI to allow reversion to wild-type virus before instituting a new regimen is not recommended because this approach has not been demonstrated to be beneficial and may be detrimental (AI).

The remaining situations in which STI can still be considered are in cases of significant antiretroviral toxic effects (AIII) and for the treatment of intercurrent infections in situations in which significant drug interactions might jeopardize the efficacy of either treatment (AII). Treatment fatigue, when a patient strongly requests that treatment be stopped temporarily (AII) is a common reason to consider an STI.

Antiretrovirals should be reinstituted once the toxicities resolve, the infection has been treated, or the patient is ready to restart treatment (BII). In the case of STI for treatment fatigue, the patient should be counseled about the risk of possible disease progression and the risk of drug resistance once therapy is stopped. If the STI is instituted, close monitoring is advised.

Antiretroviral Therapy in Special Populations

Pregnancy. The dual goals of antiretroviral therapy in pregnant women are to provide therapy for the mother and to reduce the likelihood of transmission of the virus to the fetus or neonate. Indications for therapy in pregnant women generally mirror those in other HIV-1-infected adult populations but the choices of antiretroviral agents are more limited because of concerns regarding potential teratogenicity.

Recommendations. The initiation of antiretroviral therapy during the first trimester should be avoided if possible. In general, when an HIV-1 infected woman taking effective antiretroviral therapy becomes pregnant, antiretroviral drugs should not be discontinued although an adjustment in the regimen based on the considerations outlined below may be in order. After the first trimester of pregnancy, the indications for the initiation of therapy are the same as in nonpregnant women except that therapy directed at preventing viral transmission to the fetus is generally recommended during the third trimester for all women regardless of the CD4 cell count. If antiretroviral drugs are administered to women to prevent maternofetal transmission of HIV-1, they should be given in combinations intended to be fully suppressive.

Assuming the virus is susceptible, zidovudine and lamivudine or emtricitabine are the preferred nRTIs.[99] Other nRTIs may be substituted if resistance testing indicates that drug resistance mutations are present (BIII).

An increased risk of hepatotoxicity is associated with the use of nevirapine in pregnancy, especially if initiated in women with more than 250 CD4 cells/μL.[100] In women who become pregnant while taking nevirapine, this risk is substantially lower and although close monitoring is warranted, it is not required that nevirapine be replaced in women who are receiving it without untoward effects when they become pregnant (BIII).

Until more data are available that address concerns about bone formation in utero, tenofovir should be avoided unless resistance testing suggests its use is advisable (BIII). Efavirenz is contraindicated in the first trimester of pregnancy (AII).[101-103] Nelfinavir has been used extensively in pregnancy, but concerns about its potency make it a less attractive agent than in the past (BIIa).[104]

Hepatitis B Virus Coinfection. Management of persons coinfected with HBV is complicated by 2 factors. First, several of the agents (tenofovir, lamivudine, emtricitabine) used to treat HIV are also active against HBV. Second, as HBV-specific immunity is reconstituted with successful antiretroviral therapy, severe flares of hepatocellular inflammation can occur. These flares may be particularly severe if therapy with 1 or more agents active against HBV is stopped after a period of antiretroviral therapy during which HBV-specific immunity has been restored. Flares have also been observed when HBV resistance to lamivudine or emtricitabine develops while the patient is taking antiretroviral therapy.[105-107]

Recommendations. When it is necessary to treat both HBV and HIV in coinfected patients, tenofovir and emtricitabine (or lamivudine) are the recommended nRTIs (BIII).[108,109] If a HAART regimen is started that includes lamivudine or emtricitabine but not tenofovir, addition of entecavir should be considered to avoid exposing HBV to monotherapy with either lamivudine or emtricitabine (BIII).[110]

For patients with early HIV infection for which therapy is not yet indicated but who need treatment solely for their HBV infection, adefovir or entecavir may be used with a low risk of selecting for HIV resistance mutations (BIII).[111] Entecavir appears to be more potent against HBV than adefovir, but controlled trials have not been reported in the coinfected population (BIII).

Hepatitis C Virus Coinfection. Hepatitis C virus infection complicates the treatment of HIV infection primarily because the underlying liver disease may result in more uncertainty about whether elevations in liver enzymes are due to the HCV or to the antiretroviral regimen. Despite this, there is no evidence that antiretroviral drugs are inherently more hepatotoxic in this population or that there should be a different set of considerations about which agents to use, except for patients who are receiving simultaneous ribavirin treatment of HCV.[112]

Recommendations. Selection of antiretroviral agents in the HCV-coinfected population should be made with the same considerations as those used in the HCV-uninfected population (BIII). Didanosine should be avoided in patients receiving ribavirin because of an increased risk of pancreatitis and lactic acidosis with this combination (AIIa).[113]

Race and Sex Differences. Compared with men, women have been shown to have differences in HIV viral load,[114,115] drug-related toxic effects,[116-121] and pharmacokinetics.[122-126] However, there are few data to guide decision making on choice of therapy and dosing by sex. It is increasingly important that clinical trials be designed to address issues important for the care of women with HIV and that women are enrolled in larger numbers in clinical trials.

There are no data that indicate racially based differences in the responsiveness to antiretroviral therapy.[127] A genetic polymorphism found in 20% of African Americans reduces the metabolism of efavirenz, thereby leading to higher average drug levels.[128] Although this polymorphism is associated with more adverse central nervous system events in patients taking efavirenz, its frequency in the African American population does not result in a higher rate of adverse effects necessitating drug discontinuation.[128] Conversely, the HLA-B 5701 haplotype associated with abacavir hypersensitivity in the white population is less common in the black population.[39] It is likely that other such polymorphisms will be delineated in the future, but at this point they do not dictate changes in the approach to antiretroviral chemotherapy.

Recommendation. Antiretroviral therapy decisions should be made independent of the race of the patient (BIIa).

***Mycobacterium tuberculosis* Infection.** The use of antiretroviral therapy in patients with active *Mycobacterium tuberculosis* infection is complicated by interactions between rifamycin-based antituberculous drugs and PIs or NNRTIs[129] and by the occurrence of immune reconstitution inflammatory syndrome in patients in whom treatment for the 2 infections is started in close temporal proximity—up to 30% of patients.[130,131] These reactions usually occur in the first 4 to 8 weeks after initiation of antiretroviral therapy and reflect reconstituted immunity to *M tuberculosis*. They may include systemic manifestations, such as fever and malaise, or local reactions in organs, such as the lungs and central nervous system depending on the location of the mycobacterial infection.

Recommendations. When both infections are diagnosed simultaneously, treatment for tuberculosis should be started immediately(BIII). Antiretroviral therapy should not be delayed for patients with low CD4 cell counts but a precise CD4 cell count threshold at which therapy should be delayed or an optimal interval for the delay in the start of antiretroviral therapy has not been established in controlled clinical trials (BIII).

All HIV-1-infected patients with tuberculosis should be treated with a rifamycin-based regimen. Drug selections and dosages for their antiretroviral regimens should be made with considerations for the interactions between rifamycins and antiretroviral agents (BIII).[129] These interactions are more pronounced for rifampin than for rifabutin.

Immune reconstitution inflammatory syndrome reactions are best managed with anti-inflammatory agents (including corticosteroids, if necessary; BIII). Efforts should be made to maintain both the antituberculous and antiretroviral therapy although this goal can be difficult to achieve when signs or symptoms of the immune reconstitution inflammatory syndrome overlap those that can occur with hypersensitivity reactions to 1 or more of the agents in use (BIII).

Conclusions

In the nearly 2 decades since zidovudine was introduced, 21 additional agents in 5 drug classes have been approved; potent combination therapy has become a worldwide standard of care; morbidity and mortality in the developed world have been substantially reduced, and major antiretroviral rollouts have been initiated in the developing world. Balanced against this progress is the identification of major unpredicted toxic effects and recognition of the limitations that drug class cross-resistance place on alternate treatment regimens in the setting of treatment failure.

On the horizon are investigational antiretroviral drugs in existing classes such as the NNRTIs etravirine and TMC-278, as well as drugs in novel classes. The development of CCR5 inhibitors illustrates the complexity and unpredictability of antiretroviral agent development. For example, CCR5 coreceptor antagonists have encountered challenges. Aplaviroc's development was stopped because of hepatotoxicity. Vicriviroc's development in treatment-naive patients was discontinued because of unexpected virologic failures and the drug is being carefully scrutinized to determine if lymphoma development is potentiated by the drug

in treatment-experienced persons. Maraviroc's development in both treatment-naive and treatment-experienced persons is ongoing. Encouragingly, integrase inhibitors (MK-0518 and GS-9137) are showing promise,[132,133] and proof-of-principle for the maturation inhibitor, PA-457, has been demonstrated in humans.[134] It is quite possible that paradigms of treatment will be altered by 1 or more of these agents—that is, when to start therapy and with what, may well change in the years ahead.

Given the rapid evolution of knowledge, clinicians are challenged to stay abreast of new information that can affect practice. Therapeutic choices rooted in the pathogenesis of HIV disease and individualization of therapy to maximize benefit are the principles that remain constant in a rapidly changing environment.

Author Affiliations: Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York (Dr Hammer); Department of Medicine, University of Alabama at Birmingham (Dr Saag); Department of Preventive Medicine, Universidade Federal do Rio de Janeiro, Brazil (Dr Schechter); University of British Columbia, Vancouver (Dr Montaner); Department of Medicine, University of California San Diego, San Diego (Dr Schooley); The International AIDS Society–USA, San Francisco, Calif (Ms Jacobsen); AIDS Research Consortium of Atlanta, Ga (Dr Thompson); Department of Biomedicine, Brown University School of Medicine, Providence, RI (Dr Carpenter); Department of Medicine, University of Miami School of Medicine, Fla (Dr Fischl); Department of HIV Medicine, Chelsea and Westminster Hospital, London, England (Dr Gazzard); Department of Medicine, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain (Dr Gatell); Department of Medicine, Harvard Medical School, Boston, Mass (Dr Hirsch); Departments of Medicine, Stanford University Medical Center, Stanford, Calif (Dr Katzenstein); Departments of Pathology and Medicine, University of California San Diego and San Diego Veterans Affairs Healthcare System, San Diego (Dr Richman); Department of Drug Discovery and Evaluation, Istituto Superiore di Sanità, Rome, Italy (Dr Vella); Department of Infectious Diseases, Hôpital Bichat-Claude Bernard, X. Bichat Medical School, Paris, France (Dr Yeni); Department of Medicine, University of California San Francisco and San Francisco Veterans Affairs Medical Center, San Francisco (Dr Volberding).

Financial Disclosures: Dr Carpenter reported that he has no relevant financial affiliations to disclose. Dr Fischl reported having received grants and research support from Abbott, Bristol-Myers Squibb, and GlaxoSmithKline. Dr Gatell reported having served as a scientific advisor to or has received grants and research support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Hoffman-La Roche, Johnson & Johnson, Merck, and Pfizer. Dr Gazzard reported having served as a scientific advisor to Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Johnson & Johnson and on the speakers' bureau of Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Johnson & Johnson. Dr Hammer reported having received grants and research support from Merck and having served as a scientific advisor to Boehringer Ingelheim, Progenics, Pfizer, Tibotec-Virco, and on a database monitoring board for Bristol-Myers Squibb. Dr Hirsch reported having served on data safety monitoring boards for GlaxoSmithKline and Merck, having been a consultant for Schering Plough, and having received research support from Schering Plough Takeda. Ms Jacobsen reported no relevant financial affiliations to disclose. Dr Katzenstein reported having received research and travel support and honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, and Gilead. Dr Montaner reported having received grants and research support from, serving as an ad hoc advisor to, or having spoken at events sponsored by Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Hoffmann-La Roche, Pfizer, Sanofi, Tibotec, and Trimeris. Dr Richman reported having served as a consultant to Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Merck, Monogram Biosciences, Pfizer, and Roche. Dr Saag reported having received grants and research support from Gilead, GlaxoSmithKline, Panacos, Pfizer/Agouron, Roche, Serono, and Tibotec and having served as a scientific advisor to Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Monogram Biosciences, Panacos, Pfizer/Agouron, Progenics, Roche, Tanox, Tibotec/Virco, Trimeris, and Vertex. Dr Schechter reported having received grants and research support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Pfizer, and Roche, having served as a consultant to Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Pfizer, and Roche, and having served as a scientific advisor to Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck, Pfizer, and Roche. Dr Schooley reported having served as a consultant to Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Monogram Biosciences, Roche, Tibotec, and Vertex and as a scientific advisor to Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Monogram Biosciences, Roche, Tibotec, and Vertex, and has stock options for Monogram Biosciences. Dr Thompson reported having received grants and research support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Chiron, GlaxoSmithKline, Gilead, Merck, Pfizer/Agouron, Progenics, Roche, Serono, Theratechnologies, Tibotec, Triangle, Trimeris, and VaxGen, honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Pfizer/Agouron, Roche, Serono, Tibotec, Triangle, and Trimeris, and served as a consultant or scientific advisor to Abbott, GlaxoSmithKline, Gilead, Pfizer/Agouron, Serono, Tibotec, and Triangle. Dr Vella reported having received grants and research support from Merck and has served as a scientific advisor to Gilead, Pfizer, and Tibotec, and reported receiving honoraria for lectures for Boehringer-Ingelheim and Gilead Sciences. Dr Volberding reported that he has served on the scientific advisory boards for Bristol-Myers Squibb, Merck, Schering, GlaxoSmithKline, and Pfizer, and formerly for Immune Response Corp, is on the data safety monitoring board of Incyte and the Endpoint Adjudication Committee for Schering Plough, has received honoraria from Vertex and Gilead, and has stock options for Immune Response Corp. Dr Yeni reported having received grants and research support from Bristol-Myers Squibb, GlaxoSmithKline, Merck, Roche, and Tibotec and having served as a consultant to Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, and Tibotec.

Funding/Support: This work was funded by the International AIDS Society–USA. No private sector or government funding contributed to this effort; panel members are not compensated.

Role of the Sponsor: The International AIDS Society-USA determined the need for the effort, selected the panel members, and provided administrative and financial support.

Acknowledgment: We thank Michelle Tayag, BS, an employee of IAS-USA, for administrative support in preparing the manuscript.

REFERENCES

1. Centers for Disease Control and Prevention. Kaposi's sarcoma and *Pneumocystis pneumonia* among homosexual men—New York City and California. *MMWR Morb Mortal Wkly Rep*. 1981;30:305-308.
2. Centers for Disease Control and Prevention. Twenty-five years of HIV/AIDS–United States, 1981-2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:585-589.
3. UNAIDS/WHO AIDS Epidemic Update: December 2005. Available at: http://www.unaids.org/epi/2005/doc/report.asp. Accessed: March 6, 2006.
4. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-860.
5. Emini EA. Protease inhibitors. In: Program and abstracts of the 3rd Conference on Retroviruses and Opportunistic Infections; January 28-February 1, 1996; Washington, DC. Abstract L1.
6. Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996: recommendations of an international panel. *JAMA*. 1996;276:146-154.
7. Hammer SM. Clinical practice. Management of newly diagnosed HIV infection. *N Engl J Med*. 2005;353:1702-1710.
8. Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in HIV-1 infection. *Nature*. 1995;373:117-122.
9. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4+ lymphocytes in HIV-1 infection. *Nature*. 1995;373:123-126.
10. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. *Nat Med*. 1996;2:625-629.
11. Hirsch MS, Conway B, D'Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. International AIDS Society—USA Panel. *JAMA*. 1998;279:1984-1991.
12. World Health Organization (WHO) Guidelines. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access: recommendations for a public health approach. June 2006. http://www.who.int/hiv/pub/prev_care/en/ScalingUp_E.pdf. Accessed November 13, 2003.
13. Yeni PG, Hammer SM, Hirsch MS, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA panel. *JAMA*. 2004;292:251-265.
14. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672-693.
15. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;39:1147-1171.
16. National Institutes of Health. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) Express. http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf. Accessed February 3, 2006.
17. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV

Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40:1559-1585.
18. Egger M, May M, Chene G, et al. Prognosis of HIV-1 infected drug naive patients starting potent antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*. 2002;360:119-129.
19. Lichtenstein K, Armon C, Buchacz K, et al. Early, Uninterrupted ART is associated with improved outcomes and fewer toxicities in the HIV outpatient study (HOPS). In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 769.
20. Brenchley JM, Price DA, Douek DC. HIV disease: fallout from a mucosal catastrophe? *Nat Immunol*. 2006;7:235-239.
21. Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med*. 2004;200:749-759.
22. Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. *Nature*. 2005;434:1093-1097.
23. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med*. 2004;200:761-770.
24. Phanuphak N, Apornpong T, Teeratakulpisarn S, et al. Pregnancy outcomes after combined ART or short-course AZT with single-dose nevirapine in Thai women with high and low CD4 cell counts. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 712.
25. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349:2293-2303.
26. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med*. 2004;350:1850-1861.
27. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimen for the initial treatment of HIV-1 infection (AIDS Clinical Trials Group Study–ACTG 5095): a randomized controlled trial. *JAMA*. 2006;296:769-781.
28. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS*. 2005;19:685-694.
29. Rotger M, Taffe P, Bleiber G, et al. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. *J Infect Dis*. 2005;192:1381-1386.
30. Persico M, Persico E, Bakker CT, et al. Hepatic uptake of organic anions affects the plasma bilirubin level in subjects with Gilbert's syndrome mutations in UGT1A1. *Hepatology*. 2001;33:627-632.
31. Rodriguez Novoa S, Barreiro P, Rendon A, et al. Plasma levels of atazanavir and the risk of hyperbilirubinemia are predicted by the 3435C→T polymorphism at the multidrug resistance gene 1. *Clin Infect Dis*. 2006;42:291-295.
32. Malan N, Krantz E, David N, et al. Efficacy and safety of atazanavir-based therapy in antiretroviral naive HIV-1 infected subjects, both with and without ritonavir: 48-week results from A1424-089. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colorado. Abstract 107LB.
33. Dragsted UB, Gerstoft J, Youle M, et al. A randomized trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1-infected patients: the MaxCmin2 trial. *Antivir Ther*. 2005;10:735-743.
34. Ananworanich J, Ruxrungtham K, Siangphoe U, et al. A prospective cohort study of efficacy and safety of 2 nRTIs plus once-daily ritonavir-boosted saquinavir hard gel capsule (SQV-HGC/R) at 24 weeks. In: Program and abstracts 15th International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract Poster TuPeB4469.
35. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354:251-260.
36. Gulick RM, Ribaudo HJ, Shikuma CM, et al. ACTG A5095: a comparative study of 3 protease inhibitor-sparing antiretroviral regimens for the initial treatment of HIV infection. In: Program and abstracts of the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment; July 13-16, 2003; Paris, France. Abstract 41.
37. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292:191-201.
38. Sheran M. The nonnucleoside reverse transcriptase inhibitors efavirenz and nevirapine in the treatment of HIV. *HIV Clin Trials*. 2005;6:158-168.
39. Martin AM, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci U S A*. 2004;101:4180-4185.
40. Rauch A, Nolan D, Martin A, Mckinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis*. 2006;43:99-102.
41. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*. 2004;292:180-189.
42. Cheng A, Wulfsohn M, Cheng SS, Toole JJ. 2 year long term safety profile of tenofovir DF (TDF) in treatment-experienced patients from randomized, double-blind, placebo-controlled clinical trials. In: Program and abstracts of the 9th European AIDS Conference; October 25-29, 2003; Warsaw, Poland. Abstract 7.3/7.
43. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis*. 2005;40:1194-1198.
44. Thompson M, Haubrich R, Margolis D, et al. Differences in calculated glomerular filtration rates in efavirenz- or tenofovir-treated adults in ESS40006. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 777.
45. Guest J, Rimland D, Patterson B, Desilva K. Tenofovir-induced nephrotoxicity in the first year of therapy. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colo. Abstract 778.
46. Heffelfinger J, Hanson D, Voetsch A, McNaghten A, Sullivan P. Renal impairment associated with the use of tenofovir. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 779.
47. Crane H, Harrington R, Van Rompaey S, Kitahata M. Didanosine and lower baseline body weight are associated with declining renal function among patients receiving tenofovir. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 780.
48. Nelson M, Cooper D, Schooley R, et al. The safety of tenofovir DF for the treatment of HIV infection: the first 4 years. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 781.
49. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS*. 2005;19:213-215.
50. Negredo E, Bonjoch A, Paredes R, Puig J, Clotet B. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis*. 2005;41:901-905.
51. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet*. 2004;364:65-67.
52. Podzamczer D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther*. 2005;10:171-177.
53. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS*. 2006;20:1391-1399.
54. Moyle G, Higgs C, Teague A, et al. An open-label, randomized comparative pilot study of a single-class quadruple therapy regimen versus a 2-class therapy regimen for individuals initiating antiretroviral therapy. *Antivir Ther*. 2006;11:73-78.
55. Aberg JA, Gallant JE, Anderson J, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus; recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2004;39:609-629.
56. Rizzardi GP, de Boer RJ, Hoover S, et al. Predicting the duration of antiviral treatment needed to suppress plasma HIV-1 RNA. *J Clin Invest*. 2000;105:777-782.
57. Raboud JM, Rae S, Hogg RS, et al. Suppression of plasma viral load below the detection limit of a human immunodeficiency virus kit is associated with longer virologic response than suppression below the limit of quantitation. *J Infect Dis*. 1999;180:1347-1350.
58. Raboud JM, Montaner JS, Conway B, et al. Suppression of plasma viral load below 20 copies/mL is required to achieve a long-term response to therapy. *AIDS*. 1998;12:1619-1624.
59. Macias J, Palomares JC, Mira JA, et al. Transient rebounds of HIV plasma viremia are associated with the emergence of drug resistance mutations in patients on highly active antiretroviral therapy. *J Infect*. 2005;51:195-200.
60. Hirsch MS, Brun-Vézinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type I: 2003 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. 2003;37:113-128.
61. Wensing AMJ, van de Vijver DA, Angarano G, et al. Prevalence of drug resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis*. 2005;192:958-966.
62. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team. *JAMA*. 2000;283:205-211.
63. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. 2000;283:229-234.
64. International AIDS Society-USA Resistance Mutations Project Panel. Update of the drug resistance mutations in HIV-1. Available at: http://www.iasusa.org/resistance_mutations/. Accessed: February 3, 2006.
65. Haubrich RH, Currier JS, Forthal DN, et al. A randomized study of the utility of human immunodeficiency virus RNA measurement for the management of antiretroviral therapy. *Clin Infect Dis*. 2001;33:1060-1068.
66. Katlama C, Walmsley S, Hicks C, et al. Tipranavir

achieves twice the rate of treatment responses and prolongs durability of response versus comparator PI in antiretroviral experienced patients, independent of baseline CD4+ cell count or viral load: week 48 RESIST 1 and 2 combined analyses. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colo. Abstract 520.

67. Pozniak A, Saag M, Bellos N, et al. Efficacy of TMC114/r in treatment-experienced HIV patients: factors influencing outcome in the pooled 24-week analysis of POWER 1, 2, and 3. In: Program and abstracts of the 12th Annual Conference of the British HIV Association; March 29-April 1, 2006; Brighton, England. Abstract 3.

68. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir (ATV)-based HAART in patients switched from a stable boosted or unboosted protease inhibitor (PI) treatment the SWAN Study: final results (48 weeks). In: Program and abstracts of the 10th European AIDS Conference; November 17-20, 2005; Dublin, Ireland.

69. Tavassoli N, Bagheri H, Sommet A, et al. Effects of discontinuing stavudine or protease inhibitor therapy on human immunodeficiency virus-related fat redistribution evaluated by dual-energy x-ray absorptiometry. *Pharmacotherapy*. 2006;26:154-161.

70. Sension M, Grinsztejn B, Molina J, et al. Improvement in lipid profiles after 12 weeks of switching to atazanavir from boosted or unboosted protease inhibitors in patients with no previous PI virologic failure and hyperlipidemia at baseline. In: Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Mass. Abstract 858.

71. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy of atazanavir (ATV) based HAART in patients switched from a stable PI or boosted PI (PI/r) treatment: planned week 24 analysis of a phase IIIb 48 week multicenter, open-label, randomized, prospective study, the SWAN study. In: Program and abstracts of the 3rd IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract Poster WePe6.3C15.

72. Nelson M, Arasteh K, Clotet B, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. *J Acquir Immune Defic Syndr*. 2005;40:404-412.

73. Meyer S, Hill A, De Baere I, et al. Effect of baseline susceptibility and on-treatment mutations on TMC114 and control PI efficacy: preliminary analysis of data from PI-experienced patients from POWER 1 and POWER 2. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 157.

74. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA*. 2005;293:817-829.

75. Arribas JR, Pulido F, Delgado R, et al. Lopinavir/ritonavir as a single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *J Acquir Immune Defic Syndr*. 2005;40:280-287.

76. Swindells S, DiRienzo AF, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA*. 2006;296:806-814.

77. Ananworanich J, Gayet-Agernon A, Lebraz M, et al. CD4 guided scheduled treatment interruption compared to continuous therapy: Results of the Staccato Trial. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 102.

78. Marchou B, Tangre P, Charreau I, et al. Structured treatment interruptions in HIV-infected patients with high CD4 cell counts and virologic suppression: results of a prospective, randomized, open-label trial (Window-ANRS 106). In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections: February 5-8, 2006; Denver, Colo. Abstract 104.

79. Danel C, Moh R, Sorho S, et al. The CD4-guided strategy arm stopped in a randomized structured treatment interruption trial in West-African adults: ANRS 1269 Trivacan Trial. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 105LB.

80. Palmisano L, Giuliano M, Bucciardini R, et al. Final results of a randomized, controlled trial of structured treatment interruptions vs continuous HAART in chronic HIV-infected subjects with persistent suppression of viral replication. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 103.

81. El-Sadr W, Neaton J. Episodic CD4-guided use of ART is inferior to continuous therapy: results of the SMART study. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 144.

82. Skiest D, Havlir D, Coombs R, et al. Predictors of HIV disease progression in patients who stop ART with CD4 cell counts >350 cells/mm^3. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 101.

83. Jacobson J, Saag MS. Evidence that intermittent structured treatment interruption (STI) promotes immunologic control of HIV replication: The results of AACTG 5068. In: Program and abstracts of the 3rd IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract Poster TuPe13.2B01.

84. Hicks C. RESIST-1: A phase 3, randomized, controlled, open-label, multicenter trial comparing tipranavir/ritonavir (TPV/r) to an optimized comparator protease inhibitor/r (CPI/r) regimen in antiretroviral (ARV) experienced patients: 24-week data. In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 30-November 2, 2004; Washington, DC. Abstract H-1137a.

85. Cahn P. 24-week data from RESIST 2: phase 3 study of the efficacy and safety of either tipranavir/ritonavir (TPV/r) or an optimized ritonavir (RTV)-boosted standard-of-care (SOC) comparator PI (CPI) in a large randomized multicenter trial in treatment-experienced HIV+ patients. In: Program and abstracts of the 7th International Congress on Drug Therapy in HIV Infection; November 14-18, 2004; Glasgow, Scotland. Abstract PL143.3.

86. Katlama C, Carvalho MT, Cooper D, et al. TMC114/r outperforms investigator-selected PI(s) in 3-class-experienced patients: week 24 primary analysis of POWER 1 (TMC114-C213). In Program and abstracts of the 3rd IAS Conference on HIV Pathogenesis and Treatment; July 24-27, 2005; Rio de Janeiro, Brazil. Abstract WeOaLB0102.

87. Wilkin T, Haubrich R, Steinhart CR, et al. TMC114/r superior to standard of care in 3-class-experienced patients: 24-wks primary analysis of the Power 2 Study (C202). In: Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16-19, 2005; Washington, DC. Abstract H-413.

88. Parkin NT, Chappey C. Protease mutations associated with higher or lower than expected tipranavir susceptibility based on the TPV mutation score. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 637.

89. De Meyer S, Hill A, De Baere I, et al. Effect of baseline susceptibility and on-treatment mutations on TMC114 and control PI efficacy: preliminary analysis of data from PI-experienced patients from POWER 1 and POWER 2. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colo. Abstract 157.

90. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis*. 2006;42:401-407.

91. Bonnet F, Balestre E, Bernardin E, Pellegrin JL, Neau D, Dabis F. Risk factors for hyperlactataemia in HIV-infected patients, Aquitaine Cohort, 1999-2003. *Antivir Chem Chemother*. 2006;16:63-67.

92. Lo JC, Kazemi MR, Hsue PY, et al. The relationship between nucleoside analogue treatment duration, insulin resistance, and fasting arterialized lactate level in patients with HIV infection. *Clin Infect Dis*. 2005;41:1335-1340.

93. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis*. 2005;192:1537-1544.

94. Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *N Engl J Med*. 1995;333:1662-1669.

95. Kitchen C, Suchard M, Lu J, Hoh R, Kuritzkes D, Deeks S. Continued GP41 evolution after interruption of enfuvirtide: evidence for ongoing immunologic pressure in advanced HIV disease. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections: February 5-8, 2006; Denver, Colo. Abstract 597.

96. Grabar S, Le Moing V, Goujard C, et al. Response to highly active antiretroviral therapy at 6 months and long-term disease progression in HIV-1 infection. *Acquir Immune Defic Syndr*. 2005;39:284-292.

97. Nicastri E, Chiesi A, Angeletti C, et al. Clinical outcome after 4 years follow-up of HIV-seropositive subjects with incomplete virologic or immunologic response to HAART. *J Med Virol*. 2005;76:153-160.

98. Moore DM, Hogg RS, Chan K, Tyndall M, Yip B, Montaner JS. Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response. *AIDS*. 2006;20:371-377.

99. US Department of Health and Human Services and US. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed: February 21, 2006.

100. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35:S21-S33.

101. Efavirenz capsules [package insert]. Bristol-Myers Squibb. http://www.sustiva.com. Accessed: Month 00, Accessed July 24, 2006.

102. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16:299-300.

103. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med*. 2002;162:355.

104. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002;346:2039-2046.

105. 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 with-

drawal of lamivudine. *Clin Infect Dis*. 1999;28:1032-1035.
106. Wolters LM, Niesters HG, Hansen BE, et al. Development of hepatitis B virus resistance for lamivudine in chronic hepatitis B patients co-infected with the human immunodeficiency virus in a Dutch cohort. *J Clin Virol*. 2002;24:173-181.
107. Bonacini M, Kurz A, Locarnini S, Ayres A, Gibbs C. Fulminant hepatitis B due to a lamivudine-resistant mutant of HBV in a patient coinfected with HIV. *Gastroenterology*. 2002;122:244-245.
108. Dore GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and experienced patients coinfected with HIV-1 and hepatitis B virus. *J Infect Dis*. 2004;189:1185-1192.
109. Bani-Sadr F, Palmer P, Scieux C, Molina JM. Ninety-six-week efficacy of combination therapy with lamivudine and tenofovir in patients coinfected with HIV-1 and wild-type hepatitis B virus. *Clin Infect Dis*. 2004;39:1062-1064.
110. Benhamou Y, Fleury H, Trimoulet P, et al. Antihepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology*. 2006;43:548-555.
111. Delaugerre C, Marcelin AG, Thibault V, et al. Human immunodeficiency virus (HIV) type 1 reverse transcriptase resistance mutations in hepatitis B virus (HBV)-HIV-coinfected patients treated for HBV chronic infection once daily with 10 milligrams of adefovir dipivoxil combined with lamivudine. *Antimicrob Agents Chemother*. 2002;46:1586-1588.
112. Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis*. 2005;192:992-1002.
113. Bani-Sadr F, Carrat F, Rosenthal E, et al. Spontaneous hepatic decompensation in patients coinfected with HIV and hepatitis C virus during interferon-ribavirin combination treatment. *Clin Infect Dis*. 2005;41:1806-1809.
114. Sterling TR, Lyles CM, Vlahov D, Astemborski J, Margolick JB, Quinn TC. Sex differences in longitudinal human immunodeficiency virus type 1 RNA levels among seroconverters. *J Infect Dis*. 1999;180:666-672.
115. Currier JS, Spino C, Grimes J, et al; The AIDS Clinical Trials Group 175 Team. Differences between women and men in adverse events and CD4+ responses to nucleoside analogue therapy for HIV infection. *J Acquir Immune Defic Syndr*. 2000;24:316-324.
116. Boehringer Ingelheim. *Dear Health Care Professional* [letter] . Germany: Boehringer Ingelheim Pharmaceuticals; 2004.
117. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis*. 2005;191:825-829.
118. Clark R. Sex differences in antiretroviral therapy-associated intolerance and adverse events. *Drug Saf*. 2005;28:1075-1083.
119. Kumar PN, Rodriguez-French A, Thompson MA, et al. A prospective, 96-week study of the impact of trizivir, combivir/nelfinavir, and lamivudine/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: effect of sex and ethnicity. *HIV Med*. 2006;7:85-98.
120. Santos J, Palacios R, Gonzalvo A, Ruiz J, Marquez M. Atherogenic lipid profile and cardiovascular risk factors in HIV-infected patients (Netar Study). *Int J STD AIDS*. 2005;16:677-680.
121. Van Leth F, Phanupak P, Stroes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. *PLoS Med*. 2004;1:e19.
122. Burger D, van der Heiden I, la Porte C, et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol*. 2006;61:148-154.
123. Burger DM, Siebers MC, Hugen PW, Aarnoutse RE, Hekster YA, Koopmans PP. Pharmacokinetic variability caused by gender: do women have higher indinavir exposure than men? *J Acquir Immune Defic Syndr*. 2002;29:101-102.
124. Pai MP, Schriever CA, Diaz-Linares M, Novak RM, Rodvold KA. Sex-related differences in the pharmacokinetics of once-daily saquinavir soft-gelatin capsules boosted with low-dose ritonavir in patients infected with human immunodeficiency virus type 1. *Pharmacotherapy*. 2004;24:592-529.
125. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol*. 2004;44:499-523.
126. Clark RA, Squires KE. Gender-specific considerations in the antiretroviral management of HIV-infected women. *Expert Rev Anti Infect Ther*. 2005;3:213-227.
127. Anastos K, Schneider MF, Gange SJ, et al. The association of race, sociodemographic, and behavioral characteristics with response to highly active antiretroviral therapy in women. *J Acquir Immune Defic Syndr*. 2005;39:537-544.
128. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS*. 2004;18:2391-2400.
129. Centers for Disease Control and Prevention. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/PDF/tbhiv.pdf. Accessed February 21, 2006.
130. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004;59:704-707.
131. Schluger NW, Perez D, Liu YM. Reconstitution of immune responses to tuberculosis in patients with HIV infection who receive antiretroviral therapy. *Chest*. 2002;122:597-602.
132. Grinsztejn B, Nguyen BY, Katlama C, et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 159LB.
133. DeJesus E, Berger D, Markowits M, et al. The HIV integrase inhibitor GS-9137 (JTK-303) exhibits potent antiviral activity in treatment-naive and experienced patients. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 160LB.
134. Smith P, Forrest D, Beatty G, et al. Pharmacokinetics/pharmacodynamics of PA-457 in a 10-day multiple dose monotherapy trial in HIV-infected patients. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract 52.