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*JAMA*. 2008;300(5):555-570 (doi:10.1001/jama.300.5.555)

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# Antiretroviral Treatment of Adult HIV Infection

## 2008 Recommendations of the International AIDS Society–USA Panel

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**T**HE FIELD OF ANTIRETROVIRAL therapy continues to evolve rapidly, and, to maintain the highest possible standard of care, treatment guidelines must continually be refined to assist the complex decision-making process. For a disease that has been transformed from almost uniformly fatal to manageable over decades, the impact of treatment decisions is substantial. Treatment can provide durable virologic, immunologic, and clinical benefits while minimizing toxicities and drug resistance,

**Context** The availability of new antiretroviral drugs and formulations, including drugs in new classes, and recent data on treatment choices for antiretroviral-naïve and -experienced patients warrant an update of the International AIDS Society–USA guidelines for the use of antiretroviral therapy in adult human immunodeficiency virus (HIV) infection.

**Objectives** To summarize new data in the field and to provide current recommendations for the antiretroviral management and laboratory monitoring of HIV infection. This report provides guidelines in key areas of antiretroviral management: when to initiate therapy, choice of initial regimens, patient monitoring, when to change therapy, and how best to approach treatment options, including optimal use of recently approved drugs (maraviroc, raltegravir, and etravirine) in treatment-experienced patients.

**Data Sources and Study Selection** A 14-member panel with expertise in HIV research and clinical care was appointed. Data published or presented at selected scientific conferences since the last panel report (August 2006) through June 2008 were identified.

**Data Extraction and Synthesis** Data that changed the previous guidelines were reviewed by the panel (according to section). Guidelines were drafted by section writing committees and were then reviewed and edited by the entire panel. Recommendations were made by panel consensus.

**Conclusions** New data and considerations support initiating therapy before CD4 cell count declines to less than 350/μL. In patients with 350 CD4 cells/μL or more, the decision to begin therapy should be individualized based on the presence of comorbidities, risk factors for progression to AIDS and non-AIDS diseases, and patient readiness for treatment. In addition to the prior recommendation that a high plasma viral load (eg, >100 000 copies/mL) and rapidly declining CD4 cell count (>100/μL per year) should prompt treatment initiation, active hepatitis B or C virus coinfection, cardiovascular disease risk, and HIV-associated nephropathy increasingly prompt earlier therapy. The initial regimen must be individualized, particularly in the presence of comorbid conditions, but usually will include efavirenz or a ritonavir-boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/lamivudine). Treatment failure should be identified and managed promptly, with the goal of therapy, even in heavily pretreated patients, being an HIV-1 RNA level below assay detection limits.

*JAMA. 2008;300(5):555-570*

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and potentially allow for a normal life span.

The rationale for the current update of the 2006 International AIDS So-

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### 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: Evidence from 1 or more randomized, controlled clinical trials published in the peer-reviewed literature
- Ib: Evidence from 1 or more randomized, controlled clinical trials presented in abstract form at peer-reviewed scientific meetings
- IIa: Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
- IIb: Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
- III: Recommendation based on the panel's analysis of the accumulated available evidence

ciety–USA (IAS–USA) antiretroviral treatment recommendations<sup>1</sup> is based on (1) the recent approval of 3 novel agents: maraviroc, a CC chemokine receptor 5 (CCR5) antagonist; raltegravir, an integrase strand transfer inhibitor; and etravirine, a second-generation nonnucleoside reverse transcriptase inhibitor (NNRTI); (2) new data that better inform the choice of drugs for initial therapy and the management of treatment failure; and (3) new pathogenetic insights into the role of human immunodeficiency virus (HIV) in disease processes previously considered non–AIDS-related conditions.

These guidelines are built on the precept of pathogenesis- and evidence-based individualization of therapy in

highly resourced settings. Consequently, they are most applicable to developed and selected mid-level economies. However, the core principle underlying these guidelines, namely pathogenesis-directed therapy with regimens designed to achieve full virologic suppression with minimal toxicity and maximal simplicity, is applicable to the developing world. Progress with antiretroviral rollout in the developing world is encouraging,<sup>2</sup> but recent advances in the highly resourced world need to be adapted and translated to the developing world to realize these benefits. Thus, these guidelines can be viewed in 2 contexts—providing direct, practical advice to caregivers in the developed world and serving as an advocacy tool to help close HIV treatment gaps between high and low socioeconomic settings.

### METHODS

The volunteer panel was first convened by the IAS–USA in 1995<sup>3</sup> to develop evidence-based recommendations for antiretroviral therapy in adult HIV infection in developed world settings.

After a planned partial rotation, the panel reconvened in February 2008. The panel met in person and electronically to consider data produced since its 2006 report. A MEDLINE search was conducted (P.A.V.) to identify relevant studies. All manufacturers of approved or expanded-access antiretroviral drugs were contacted for published or publicly presented data pertaining to their product(s). Data on file, unpublished observations, personal communications, and other such information was not considered except for public releases of data and safety monitoring board reports. Where recommendations have not changed, reference to supporting evidence is available in the previous report.<sup>1</sup> Each panel member was assigned to 1 or more writing teams, and section leaders (J.J.E., P.R., R.T.S., M.A.T., and S.W.) prepared drafts as previously described.<sup>1</sup>

The quality and strength of the evidence were rated according to a scale

(BOX).<sup>1</sup> Clinical recommendations were made by panel consensus.

### WHEN TO START ANTIRETROVIRAL THERAPY Established HIV-1 Infection

The primary goal of antiretroviral therapy is to increase disease-free survival through maximal suppression of viral replication and preservation of immunologic function. The optimal timing of initiation of antiretroviral therapy depends on consideration of these benefits in balance with the risks of drug toxicity, potential emergence of viral resistance, and the understanding that HIV infection is a chronic disease requiring continuous therapy, usually over the course of decades.

Although the benefits of beginning antiretroviral therapy at CD4 cell counts above 200/ $\mu$ L are well documented, previous recommendations were influenced by the perceived need to minimize drug toxicity and preserve therapeutic options for subsequent regimens.<sup>1</sup> Although these remain crucial concerns, as treatment options have increased and the risks of untreated viremia are better appreciated, the risk-benefit ratio is shifting toward earlier treatment.

The substantial toxicity and inconvenience of early regimens dampened enthusiasm for starting therapy at higher CD4 cell counts. However, newer regimens are potent, durable, and less toxic.<sup>4–10</sup> Fixed-dose combinations with long half-lives and ritonavir-boosted protease inhibitors (PIs) have simplified regimens, improved pharmacokinetics and treatment response,<sup>11</sup> enhanced adherence to therapy,<sup>12</sup> and slowed the emergence of resistance.<sup>11,13,14</sup>

New data demonstrate the increased relative burden of non-AIDS diseases in HIV-infected persons and require their inclusion in the definition of HIV disease progression.<sup>15–21</sup> Clinical trial and observational cohort data indicate that even at high CD4 cell counts, uncontrolled HIV replication and immune activation are strongly associated with the development of diseases not traditionally associated with HIV infection, such as non-

AIDS cancers (including lung, anal, and head and neck cancers and Hodgkin lymphoma)<sup>22-24</sup> and end-organ damage, including cardiovascular,<sup>25</sup> hepatic,<sup>26</sup> and renal<sup>27,28</sup> dysfunction. A large multicohort survival analysis among antiretroviral-naive persons with CD4 cell counts of more than 350/ $\mu$ L demonstrated increased mortality even at high CD4 cell counts compared with the general population.<sup>29</sup> The risk of developing non-AIDS-defining cancers is higher when the CD4 cell count is less than 500/ $\mu$ L for 1 year or more.<sup>30</sup> Markers of inflammation (eg, interleukin 6) and coagulation (eg, D dimer) are strong predictors of mortality, even at higher CD4 cell counts, and are tightly correlated with plasma HIV-1 RNA levels.<sup>31-33</sup> In addition, maintaining CD4 cell counts of more than 500/ $\mu$ L may result in a normal life expectancy through the prevention of irreversible immune damage associated with prolonged immune activation.<sup>34</sup>

Although not designed to address the issue of when to initiate therapy, recent evidence from the Strategic Management of Antiretroviral Therapy (SMART) trial supports the hypothesis that uncontrolled viral replication carries an increased risk of morbidity and mortality at all CD4 strata.<sup>35</sup> In this trial, opportunistic diseases and death occurred at higher rates when therapy was interrupted than when therapy was continuous, even with CD4 cell counts of more than 350/ $\mu$ L. At high CD4 cell counts, these outcomes were associated with HIV-1 RNA levels above 400 copies/mL. The risks of cardiovascular, hepatic, and renal complications also were higher in the drug interruption group than in the continuous viral suppression group.<sup>36</sup> When therapy was reinstated, risk decreased but did not return to baseline.<sup>37</sup> In a subset of patients who were antiretroviral-naive or not currently receiving therapy, those in the deferred therapy group had an increased rate of serious non-AIDS events compared with those in the immediate group who began treatment with CD4 cell counts of more than 350/ $\mu$ L.<sup>38</sup> These results demonstrate a strong relationship between uncontrolled HIV

replication and multiple non-AIDS-defining diseases that substantially affect both quality and length of life, even at CD4 cell counts of more than 350/ $\mu$ L. Treatment for all infected persons with HIV-related symptoms and for all asymptomatic HIV-infected persons with CD4 cell counts at or less than 200/ $\mu$ L has been a consistent recommendation.<sup>1</sup> Additionally, longitudinal cohort studies and randomized clinical trials have shown that those who begin therapy with CD4 cell counts between 200/ $\mu$ L and 350/ $\mu$ L have lower rates of AIDS-defining diseases and death and are more likely to achieve maximal suppression of virus replication and higher CD4 cell counts than those who begin therapy at lower CD4 cell levels.<sup>19,34,39-52</sup> Although not all persons with higher CD4 cell counts are appropriate candidates for treatment, these data support the benefit of therapy, especially when other comorbidities or risk factors for HIV disease progression exist. In particular, high viral load (ie, >100 000 copies/mL), rapid CD4 cell count decline (>100/ $\mu$ L per year), hepatitis B or C virus (HBV or HCV) coinfection, HIV-associated nephropathy (HIVAN), and risk factors for non-AIDS diseases, particularly cardiovascular diseases, merit consideration of initiation of therapy independent of CD4 cell counts.

Other benefits of antiretroviral therapy include decrease of mother-to-child HIV transmission<sup>53</sup> and potential reduction of HIV transmission among adults.<sup>34</sup> Because antiretroviral therapy can decrease HIV transmission in the setting of couples with discordant HIV status,<sup>55,56</sup> consideration should be given to initiation of therapy in the HIV-seropositive partner but should not supplant traditional prevention methods. Risk reduction counseling should be a routine part of care and reinforced at each clinician-patient interaction.

### Primary HIV-1 Infection

Although knowledge continues to evolve regarding the pathogenesis of primary HIV infection, no definitive evi-

**Table 1.** Recommendations for Initiating Antiretroviral Therapy in Treatment-Naive Adults With Established HIV-1 Infection<sup>a</sup>

Measure	Recommendation (Rating)
Symptomatic HIV disease	Antiretroviral therapy recommended (A1a)
Asymptomatic HIV disease	
CD4 cell count <350/ $\mu$ L	Antiretroviral therapy recommended (AIIa, AIIb)
CD4 cell count $\geq$ 350/ $\mu$ L	Antiretroviral therapy should be individualized (see "When to Start" section of text) (AIIa, AIIb) <sup>b</sup>

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup>In nonpregnant adults only. For all individuals, regardless of whether they are receiving treatment, intensive counseling to prevent secondary transmission is recommended.

<sup>b</sup>Considerations include high viral load (>100 000 HIV RNA copies/mL), rapid decline in CD4 cell count (>100/ $\mu$ L per year), high risk of cardiovascular disease, active hepatitis B or C virus coinfections, or presence of HIV-associated nephropathy.

dence has emerged that supports routine initiation of antiretroviral therapy in primary HIV infection.

### Recommendations

The patient's readiness for treatment should always be assessed when considering initiation of therapy. Therapy is recommended (TABLE 1) for all patients with symptomatic established HIV disease (rating A1a in the Box) after appropriate counseling. For asymptomatic individuals, therapy should be initiated before the CD4 cell count decreases to less than 350/ $\mu$ L (AIIa, AIIb). At present, there are no definitive randomized clinical trial data to define a specific CD4 cell count threshold of 350/ $\mu$ L or more for beginning therapy. Therefore, in this group, decisions should be based on comorbidities, risk of disease progression (including risk of non-AIDS diseases), and patient willingness and estimated ability to adhere to long-term treatment. Rapid decline in CD4 cell count (ie, >100/ $\mu$ L per year), a plasma HIV-1 RNA level greater than 100 000 copies/mL, and risk factors for cardiovascular and other non-AIDS diseases are indicators that favor earlier therapy (AIIa, AIIb). Risk

factors for cardiovascular disease, such as hypertension, hyperlipidemia, diabetes, and tobacco use, should be aggressively managed in all patients. Although controlled clinical trials have not directly addressed whether earlier initiation of antiretroviral therapy might reduce cardiovascular or other non-AIDS-related disease risks, it is clear that the risk is higher when viral replication is uncontrolled. Patient readiness, drug interactions, adherence challenges, toxicities, and costs should be considered when determining whether to initiate therapy at higher CD4 cell counts, recognizing that treatment must be sustained. There is no upper CD4 cell limit for starting therapy when 1 or more of these considerations are present. An individual risk-benefit assessment is appropriate in such circumstances. Clinicians should follow routine screening recommendations for malignancies, implementing earlier screening when risk factors warrant it. Because infected individuals continue to be identified at an advanced stage of disease, implementing routine voluntary HIV testing and counseling using rapid testing technology is important for the earlier identification and treatment of HIV infection.

## WHAT TO START

### Recent Data: Choice of Initial Regimen

The initial selection of an antiretroviral regimen depends on the drug susceptibility of the individual patient's HIV. Transmission of resistant variants in developed countries ranges from 5% to 20%.<sup>57,58</sup> The selection is additionally influenced by factors like pill burden, frequency of dosing, anticipated tolerability, comorbid conditions, and short- and long-term adverse event profiles. Potential for emergence of resistance during therapy and subsequent treatment options may also affect the design of an initial regimen.

**PI vs NNRTI Comparisons.** AIDS Clinical Trials Group (ACTG) study A5142 compared 3 initial regimens in 757 patients: efavirenz plus 2 nRTIs, ritonavir-boosted lopinavir (lopinavir/r) plus

2 nRTIs, and efavirenz plus lopinavir/r without nRTIs. Efavirenz plus 2 nRTIs led to a longer time to virologic failure and a lower rate of virologic failure than lopinavir/r plus 2 nRTIs (24% vs 37%, respectively).<sup>59</sup> Eighty-nine percent of patients initiating efavirenz plus 2 nRTIs had HIV RNA levels of less than 50 copies/mL at 96 weeks compared with 77% of those initiating lopinavir/r plus 2 nRTIs. The CD4 cell count increases at 96 weeks were greater in patients taking lopinavir/r plus 2 nRTIs than in those taking efavirenz plus 2 nRTIs (287/ $\mu$ L vs 230/ $\mu$ L, respectively). Grade 3 or 4 diarrhea and triglyceride changes occurred more often in the group taking lopinavir/r plus 2 nRTIs, whereas lipase elevations of this severity were more common with efavirenz plus 2 nRTIs. Increases in median total cholesterol, non-high-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels were similar in the 2 nRTI-containing groups, whereas increases in triglyceride levels were lower with efavirenz plus 2 nRTIs.<sup>60</sup> Fat loss was most pronounced when efavirenz was combined with stavudine or zidovudine. There is no evidence that efavirenz combined with nonthymidine nRTIs is associated with lipoatrophy.<sup>61</sup>

**NNRTI-Based Regimens.** The virologic response of regimens containing efavirenz plus 2 nRTIs is durable<sup>59,62,63</sup> and consistent across viral load and CD4 cell count strata.<sup>64</sup> In a retrospective study examining the activity of efavirenz plus 2 nRTIs across broad CD4 and HIV RNA strata, time to virologic failure did not differ for patients with pretreatment viral loads above 300 000 RNA copies/mL and CD4 cell counts of less than 50/ $\mu$ L compared with all other patients.<sup>65</sup> Although sample sizes were limited, patients with baseline HIV RNA levels of more than 750 000 copies/mL had similar treatment responses.

**PI-Based Regimens (TABLE 2).** In an open-label, randomized study, fosamprenavir/r twice daily was noninferior to lopinavir/r twice daily.<sup>13</sup> Treatment responses were similar for those with viral loads of at least vs less than 100 000 copies/mL and across CD4 cell count strata.

Virologic failures were uncommon (6%-7%) and no major PI resistance-associated mutations were observed.

Atazanavir/r was also noninferior to lopinavir/r at 48 weeks in an open-label study. Fewer patients in either group achieved an HIV RNA level of less than 50 copies/mL if their baseline HIV RNA level was at least 100 000 copies/mL. Patients with lower CD4 cell counts appeared to respond less well to lopinavir/r. The percentage changes in total cholesterol and triglyceride (but not low- or high-density lipoprotein cholesterol) levels were greater in the lopinavir/r group.<sup>66</sup>

Darunavir/r was compared with lopinavir/r at 48 weeks in a randomized, open-label study.<sup>68</sup> Lopinavir/r could be administered once (<25% of patients) or twice daily; only 2% initiated treatment with the tablet formulation of lopinavir/r. The darunavir/r dose was 800 mg/100 mg once daily, not the currently approved dose of 600 mg/100 mg twice daily for treatment-experienced patients. The difference between groups in response to less than 50 HIV-1 RNA copies/mL at 48 weeks favoring the darunavir regimen met criteria for noninferiority but not for superiority. In the HIV RNA stratum of 100 000 copies/mL or greater, the response in the darunavir/r group was superior to that in the lopinavir/r group. Differences between the groups appeared to be driven by the response in patients who received lopinavir/r once daily. No patients acquired major PI resistance mutations. Saquinavir/r was also noninferior to lopinavir/r in a randomized, open-label study.<sup>67</sup>

Use of the soft-gel formulation of lopinavir/r, which will soon no longer be available, complicates the interpretation of the aforementioned studies. A randomized, open-label study compared once-daily vs twice-daily lopinavir/r combined with tenofovir and emtricitabine.<sup>69</sup> An 8-week comparative trial of soft-gel capsules with tablets was embedded in the overall trial, although all patients received the tablet formulation after 8 weeks. The once-daily group was noninferior to the twice-daily group, in contrast with the

comparative study of lopinavir/r and darunavir/r, and no substantial differences in treatment responses were seen between HIV RNA strata (<100 000 and ≥100 000 copies/mL). There were no differences in tolerability or adverse events.

In a smaller randomized study, there were fewer virologic failures and less re-

sistance emergence with atazanavir/r (300 mg/100 mg once daily) than with unboosted atazanavir (400 mg once daily), both combined with 2 nRTIs. Differences in the median changes in lipids were small.<sup>70</sup>

Since the previous guidelines, once-daily fosamprenavir, 1400 mg, with ritonavir, 100 mg, was approved for use in

treatment-naive patients, although comparative data are limited. A small randomized trial comparing fosamprenavir/r with atazanavir/r once daily, both with fixed-dose combination tenofovir/emtricitabine, found no substantial differences between the groups.<sup>71</sup>

**Dual nRTI Components.** Dual nRTIs remain the backbone of most initial

**Table 2.** Selected Comparative Studies of Ritonavir-Boosted Protease Inhibitors<sup>a</sup>

Source	No. of Patients	No. of Patients With <50 HIV RNA Copies/mL at 48 wk, %	Comments
Eron et al, <sup>13</sup> 2006 (KLEAN) <sup>b</sup>	878		Similar results in viral load (≥ or <100 000 copies/mL) and CD4 strata Similar adverse events
Fosamprenavir, 700 mg twice daily + ritonavir, 100 mg twice daily		66	
Lopinavir, 400 mg twice daily + ritonavir, 100 mg twice daily <sup>c</sup>		65	
Molina et al, <sup>66</sup> 2008 (CASTLE) <sup>d</sup>	883		Percentage with <50 HIV RNA copies/mL was 8%-9% less in each treatment group in stratum with ≥100 000 copies/mL; no substantial differences between groups in either viral load stratum Decreased response to lopinavir in lower CD4 strata Hyperbilirubinemia more common with atazanavir Nausea, diarrhea, elevated total cholesterol and triglyceride levels more common with lopinavir
Atazanavir, 300 mg once daily + ritonavir, 100 mg once daily		78	
Lopinavir, 400 mg once daily + ritonavir, 100 mg once daily <sup>c</sup>		76	
Walmsley et al, <sup>67</sup> 2007 (GEMINI) <sup>d</sup>	337		Results by viral load strata not reported More diarrhea and greater increases in triglycerides with ritonavir-boosted lopinavir
Saquinavir, 1000 mg twice daily + ritonavir, 100 mg twice daily		65	
Lopinavir, 400 mg twice daily + ritonavir, 100 mg twice daily <sup>c</sup>		64	
Clumeck et al, <sup>68</sup> 2007 (ARTEMIS) <sup>d</sup>	689		Most received capsule formulation of lopinavir; <25% used lopinavir once daily Treatment response was lower in both groups in stratum with ≥100 000 HIV RNA copies/mL; in this stratum, darunavir was superior ( <i>P</i> < .05) Diarrhea less frequent and mean triglyceride levels lower with darunavir
Darunavir, 800 mg once daily + ritonavir, 100 mg once daily		84	
Lopinavir, 400 mg twice daily + ritonavir, 100 mg twice daily or lopinavir, 800 mg once daily + ritonavir, 200 mg once daily		78	
Gathe et al, <sup>69</sup> 2008 (M05-730)	664		No significant difference between groups by viral load strata (< or ≥100 000 HIV RNA copies/mL) or CD4 strata No substantial differences in tolerability or laboratory adverse events
Lopinavir, 800 mg once daily + ritonavir, 200 mg once daily		77	
Lopinavir, 400 mg twice daily + ritonavir, 100 mg twice daily		76	

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup>In each study, noninferiority of the comparator group (listed first) was established.

<sup>b</sup>All patients received fixed-dose combination abacavir/lamivudine, 600 mg/300 mg once daily.

<sup>c</sup>Capsule formulation of lopinavir/ritonavir.

<sup>d</sup>All patients received fixed-dose combination tenofovir/emtricitabine, 300 mg/200 mg once daily.

regimens. Extensive data support inclusion of lamivudine or emtricitabine as 1 of the 2 nRTIs. Tenofovir/emtricitabine and abacavir/lamivudine are taken once daily. Long-term data for tenofovir/emtricitabine support its use in initial therapy,<sup>61-63</sup> although individuals with underlying renal dysfunction or requiring other nephrotoxic agents may be at increased risk of renal toxicity. Modest decreases in bone density have been observed,<sup>63</sup> and hypophosphatemia can occur.<sup>72</sup> The long-term impact of tenofovir on bone metabolism, phosphate metabolism,<sup>73</sup> and renal function needs further evaluation. Tenofovir, emtricitabine, and efavirenz are coformulated in a single pill taken once daily.

Abacavir/lamivudine is currently being compared with tenofovir/emtricitabine in a randomized, blinded, 96-week clinical trial of 688 treatment-naive patients.<sup>10</sup> Both dual-nRTI combinations are paired with once-daily lopinavir/r. At the 48-week primary end-point analysis, 68% of patients receiving abacavir/lamivudine and 67% of those receiving tenofovir/emtricitabine had HIV RNA levels of less than 50 copies/mL. In the stratum with screening viral loads of 100 000 copies/mL or greater, 63% and 65% of patients had HIV RNA levels below 50 copies/mL in the abacavir and tenofovir groups, respectively; confirmed virologic failure occurred in 12% and 11%, respectively, of the patients over 48 weeks. Median changes in triglyceride and low-density lipoprotein cholesterol levels were greater in the abacavir group.

In contrast with these results, the ongoing ACTG A5202 study of approximately 1800 treatment-naive patients comparing the same 2 dual-nRTI combinations, in conjunction with a comparison of efavirenz with atazanavir/r, was modified when a data and safety monitoring board interim review noted a higher rate of virologic failure in patients with screening viral loads of 100 000 copies/mL or higher in the abacavir/lamivudine group than in the tenofovir/emtricitabine group. The estimated hazard ratio for cumulative virologic failure in this stratum was 2.33

(95% confidence interval [CI], 1.46-3.72;  $P = .0003$ ) ([http://www.aactg.org/news\\_results.asp](http://www.aactg.org/news_results.asp)).

A large, collaborative cohort study investigated the association of nRTI use with subsequent myocardial infarction.<sup>74,75</sup> After controlling for numerous factors, an increased risk of myocardial infarction associated with recent abacavir or didanosine use (relative rates, 1.90 [95% CI, 1.47-2.45] and 1.49 [95% CI, 1.14-1.95], respectively) was demonstrated. Cumulative exposure was not predictive, and those who had not taken abacavir or didanosine for 6 months or more did not have an increased risk. The overall absolute risk was small but was greatest in those at highest risk of myocardial infarction, based on traditional cardiovascular risk factors. Although an association has been demonstrated in this study, causation is not established.

**Other Initial Combinations.** The ACTG A5142 study included an nRTI-sparing group of efavirenz, 600 mg once daily, with lopinavir, 533 mg/ritonavir, 133 mg, twice daily<sup>59</sup> that had a time to virologic failure similar to efavirenz plus 2 nRTIs in the overall analysis, although in the stratum of 100 000 HIV RNA copies/mL or greater, the time to virologic failure was shorter. Limb-fat increase was greatest in the efavirenz/lopinavir/r group, laboratory toxicity was more common (predominantly because of rises in triglyceride levels), and emergence of resistance was more frequent than in the 2 nRTI groups.

Initial PI monotherapy has also been evaluated in a small, randomized, open-label study comparing lopinavir/r alone with lopinavir/r plus zidovudine and lamivudine in patients with baseline viral loads below 100 000 copies/mL.<sup>76</sup> Fewer patients receiving PI monotherapy achieved HIV RNA levels below the limit of detection, and a greater number receiving PI monotherapy had emergence of PI resistance mutations, suggesting that this approach should currently be considered suboptimal.

In another randomized, open-label study of 114 patients, 4 nRTIs (zidovudine, lamivudine, abacavir, and te-

nofovir) had similar antiretroviral activity as efavirenz plus zidovudine and lamivudine; 68% and 67% had HIV RNA levels of less than 50 copies/mL at 48 weeks, respectively.<sup>77</sup>

**New Drug Classes in Initial Therapy.** Raltegravir, an integrase strand transfer inhibitor,<sup>78</sup> was approved in 2007 for use in highly treatment-experienced patients.<sup>79,80</sup> It was compared with efavirenz in treatment-naive patients in a randomized, partially blinded trial in which patients received 1 of 4 doses of raltegravir (100, 200, 400, or 600 mg twice daily) or efavirenz, each combined with tenofovir and lamivudine. At 48 weeks, the proportions of individuals who had an HIV RNA level of less than 50 copies/mL were similar among the 5 groups, ranging from 83% to 88%.<sup>81</sup> Phase 3 studies comparing raltegravir, 400 mg twice daily, with efavirenz once daily, each paired with 2 nRTIs, are under way.

Maraviroc, a CCR5 antagonist approved in 2007 for use in treatment-experienced patients, has antiretroviral activity only in patients with HIV-1 variants that exclusively use the CCR5 coreceptor (termed R5 viruses). Maraviroc was compared with efavirenz, each combined with zidovudine/lamivudine, in a randomized, double-blind, phase 3 study in treatment-naive patients with R5 virus.<sup>82</sup> At 48 weeks, 69.3% and 65.3% of patients achieved a viral load of less than 50 copies/mL in the efavirenz and the maraviroc groups, respectively; the prespecified criterion for noninferiority was not met.

## Recommendations

Two nRTIs plus either efavirenz (A1a) or a PI/r (A1a, A1b) are recommended for initial therapy (TABLE 3). Simplicity of therapy, pill number, tolerability, desire for pregnancy, drug interactions, primary drug resistance, and comorbid conditions are likely to influence the choice between these 2 recommended options. Efavirenz is not recommended for women in the first trimester of pregnancy or who are contemplating pregnancy (A1a). Treatment for patients with transmitted drug

resistance should be guided by resistance test results (BIIa, BIIb). Nevirapine is an alternative to efavirenz when an NNRTI-based regimen is desired and the CD4 cell count is less than 250/ $\mu$ L and 400/ $\mu$ L in women and men, respectively (AIIa).

Of the ritonavir-boosted PIs, recommended components include lopinavir/r (AIIa), atazanavir/r (AIIb), fosamprenavir/r (AIIa), darunavir/r (AIIb), or saquinavir/r (AIIb). Choice of PI/r is influenced by factors such as frequency

of dosing, pill number, coformulation, need for refrigeration, adverse effect profile, concomitant medications, comorbid illnesses, presence of primary drug resistance, and cost.

Lopinavir/r has been the most extensively studied ritonavir-boosted PI and served as the comparator for most clinical trials of other ritonavir-boosted PIs. It is the only coformulated boosted PI option, and the combination tablet does not require refrigeration. It may be given once (BIIa,

AIIb) or twice (AIIa, AIIb) daily in treatment-naïve patients, may be the most likely to cause diarrhea, and may have the greatest negative effect on triglyceride levels.

Once-daily ritonavir-boosted atazanavir (AIIb) has similar activity to lopinavir/r, with fewer gastrointestinal adverse effects, a more favorable lipid profile, and a lower pill burden.<sup>66</sup> Coadministration with acid-reducing agents must be done cautiously.<sup>86,87</sup> Fosamprenavir/r may be given twice daily (AIIa)<sup>13</sup>

**Table 3.** Recommended Components of Initial Antiretroviral Therapy and Considerations for Choosing a Regimen

Component	Considerations for Choice	Major Toxic Effects and Cautions
Nucleoside reverse transcriptase inhibitors <sup>a</sup>		
Tenofovir/emtricitabine <sup>b,c</sup>	Well tolerated Efficacy superior to zidovudine/lamivudine <sup>4,62</sup> and similar to stavudine/lamivudine <sup>63</sup> Available as a once-daily fixed dose	Baseline renal function should be evaluated before initiating tenofovir Reduce dose or avoid in patients with renal dysfunction
Abacavir/lamivudine <sup>d</sup>	Noninferior to tenofovir/emtricitabine in 1 trial <sup>10</sup> May have less activity in patients with viral load $\geq 100\,000$ HIV RNA copies/mL <sup>63</sup> Available as a once-daily fixed dose	Hypersensitivity syndrome in 5% to 8% of persons (risk associated with HLA-B*5701 genotype) Risk reduced with HLA-B*5701 screening <sup>84,85</sup> May be associated with increased risk of myocardial infarction <sup>74,75</sup>
Nonnucleoside reverse transcriptase inhibitors <sup>e</sup>		
Efavirenz	Standard-of-care comparator in many trials Available as a once-daily fixed dose with tenofovir/emtricitabine	Central nervous system toxicity may be limiting Potentially teratogenic in first trimester of pregnancy Associated with lipodystrophy when given with thymidine reverse transcriptase inhibitors <sup>60</sup>
Ritonavir-boosted protease inhibitors <sup>f</sup>		
Lopinavir	Substantial clinical trial data and phase 4 experience supporting efficacy Heat-stable tablet 1 or 2 doses per day for treatment-naïve patients	Gastrointestinal adverse effects Hyperlipidemia, especially hypertriglyceridemia
Atazanavir	Noninferior to ritonavir-boosted lopinavir Less hyperlipidemia and diarrhea <sup>66</sup> Once-daily dosing	Hyperbilirubinemia (UGT1A1-28 alleles and T3435C polymorphism in <i>MDR1</i> gene) Occasionally associated with nephrolithiasis Acid-reducing agents decrease atazanavir concentrations; proton pump inhibitors should be used cautiously
Fosamprenavir	Noninferior to ritonavir-boosted lopinavir <sup>13</sup> Once-daily or twice-daily dosing possible; more robust data with twice-daily dose	Similar adverse effect profile to ritonavir-boosted lopinavir Rash
Darunavir	Noninferior to ritonavir-boosted lopinavir and superior in those with viral load $\geq 100\,000$ HIV RNA copies/mL Less nausea, lower triglyceride levels <sup>68</sup> 800 mg + 100 mg ritonavir once daily	Rash
Saquinavir	Noninferior to ritonavir-boosted lopinavir, with lower triglyceride levels. <sup>67</sup> Twice-daily dosing	High pill burden

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup>Zidovudine/lamivudine is considered an alternative (see "When to Start" section of text).

<sup>b</sup>A baseline urinalysis and estimation of creatinine clearance or glomerular filtration rate for assessment of renal function are recommended.<sup>27</sup> All patients receiving tenofovir should be observed for development of renal dysfunction.

<sup>c</sup>Or lamivudine.

<sup>d</sup>Or emtricitabine.

<sup>e</sup>Nevirapine (in women with  $<250$  CD4 cells/ $\mu$ L and men with  $<400$  CD4 cells/ $\mu$ L) is considered an alternative (see "What to Start" section of text).

<sup>f</sup>Substantial clinical trial data exist for ritonavir-boosted lopinavir as initial antiretroviral therapy, including data on long-term outcomes. Each of the other ritonavir-boosted protease inhibitors has been compared with ritonavir-boosted lopinavir but not with one another. Choice of ritonavir-boosted protease inhibitor should be individualized (see "What to Start" section of text).

or once daily with either 200 or 100 mg of ritonavir (BIa). With twice-daily dosing, the adverse effect profile and lipid effects are similar to lopinavir/r.<sup>13</sup> Twice-daily saquinavir/r (AIb) was also noninferior to twice-daily lopinavir/r,<sup>67</sup> with less diarrhea and more favorable triglyceride changes.

Once-daily darunavir/r (AIb) is also well tolerated, with similar activity to lopinavir/r.<sup>68</sup> At present, the formulation of darunavir studied in the phase 3 trial is not available. Using darunavir/r in initial therapy must be balanced against its proven efficacy in patients with multidrug-resistant virus. Debate exists whether darunavir should be used in patients with drug-susceptible virus or should be reserved for patients with primary or acquired drug resistance.<sup>88-91</sup>

Unboosted PIs are not recommended. However, consideration of their use arises in highly selected circumstances; eg, in individuals who are not candidates for NNRTI-based therapy or who have intolerance or contraindications to ritonavir. Atazanavir, fosamprenavir, and, in some cases, nelfinavir are candidates to consider, but a non-PI-, non-NNRTI-based regimen such as raltegravir plus 2 nRTIs is another alternative, pending results of phase 3 studies.

Recommended nRTIs in the initial regimen are the fixed-dose combinations tenofovir/emtricitabine (AIa) or abacavir/lamivudine (AIa). Data published or presented since the 2006 publication of these guidelines continue to support the efficacy and safety of tenofovir/emtricitabine. The recently reported association of abacavir with an increased risk of myocardial infarction should be considered in patients with known or high risk of cardiovascular disease. The diminished virologic efficacy of abacavir/lamivudine compared with tenofovir/emtricitabine (each in combination with efavirenz or atazanavir/ritonavir) in patients with viral loads of more than 100 000 copies/mL reported in 1 randomized study should also be considered. The data are as yet insufficient,

however, to remove abacavir as a recommended nRTI component of initial therapy.

Zidovudine/lamivudine twice daily is an alternative dual-nRTI component (AIa), although the gastrointestinal and central nervous system adverse effects and associations with lipoatrophy and anemia make this choice less desirable.

The quadruple nRTI combination of abacavir/lamivudine/zidovudine/tenofovir (BIIa)<sup>77</sup> may be considered in special circumstances, such as coadministration with tuberculosis therapy or when comorbid conditions mandate treatment with other medications that have substantial drug interactions with NNRTIs and PIs. Lopinavir/r plus efavirenz (AIa)<sup>59</sup> also may be considered to avoid nRTI use, although lipid abnormalities are common. Currently, initial therapy with raltegravir should be considered only in highly selected circumstances (BIa). Use of maraviroc (CIb) or PI/r monotherapy (CIa) for initial therapy is not currently recommended.

## PATIENT MONITORING

### Considerations

Recommendations for the initial workup of newly diagnosed HIV-infected persons have not changed substantially except that baseline genotypic testing for resistance should be performed in all treatment-naïve patients regardless of estimated duration of infection.<sup>92</sup> Baseline and periodic CD4 cell counts and plasma HIV-1 RNA measurements guide timing of initial therapy. Presence of HBV or HCV infection, evidence of HIVAN, or cardiovascular risk may also influence therapy initiation and regimen and, therefore, should be assessed.

### Monitoring Treatment Response

Effective therapy should generally result in at least a 10-fold (1.0 log<sub>10</sub>) decrease in HIV-1 RNA copies/mL in the first month and suppression to less than 50 copies/mL by 24 weeks, depending on pretreatment viral load.<sup>1</sup> Once HIV-1 RNA suppression is confirmed, it should be assessed at regular intervals

(eg, every 3 or 4 months).<sup>1</sup> Isolated episodes of low-level viremia (“blips”) are not predictive of subsequent virologic failure, but consistent elevations to more than 50 copies/mL meet a strict definition of virologic failure. Confirmed viral load rebound should prompt a careful evaluation of regimen tolerability, drug-drug interactions, and patient adherence. CD4 cell counts should generally be assessed in concert with viral load. Once CD4 cell counts are consistently at least 350/μL, however, less frequent monitoring of CD4 cell count (ie, every 6 months) is reasonable if the viral load remains suppressed.

### Resistance Testing

Updated IAS-USA guidelines for the use of antiretroviral drug resistance testing have been published.<sup>92</sup> For treatment failure with HIV-1 RNA levels of more than 500 to 1000 copies/mL, resistance testing is essential and should be performed while the patient is taking the failing regimen.<sup>92</sup>

### Tropism

Human immunodeficiency virus 1 requires a second receptor, either CCR5 or CX chemokine receptor 4 (CXCR4), to enter CD4 cells. Virus may exclusively use either CCR5 (R5 virus) or CXCR4 (X4 virus) or may use both receptors (dual-tropic). Human immunodeficiency virus 1 variants within an infected individual may be R5 only, X4 only, or a mixture of R5, X4, and dual-tropic variants (so-called dual-/mixed-tropic populations). Most transmitted variants are R5, and R5 virus predominates early in the course of infection. The CCR5 antagonist maraviroc inhibits R5 virus and can provide added virologic activity in patients with R5 virus<sup>93</sup>; it has little or no activity in patients with dual-/mixed- or X4-tropic virus.<sup>94</sup> Thus, assessment of tropism prior to use of maraviroc is essential.<sup>92,95</sup>

### Monitoring for Treatment Toxicity

When balancing the risks and benefits associated with a particular treat-

ment, it is important to realize that cardiovascular, hepatic, and renal complications may not only reflect drug toxicity but may also be associated with uncontrolled HIV replication.<sup>36-39</sup> Appropriate clinical and laboratory assessment of relevant comorbid conditions should be performed before initiating treatment and during follow-up. For example, cardiovascular disease risks should be assessed by available algorithms. The Framingham risk algorithm may be the most appropriate, although it can underestimate cardiovascular disease risk in the setting of HIV infection.<sup>96</sup> Guidelines for the prevention and management of metabolic complications in HIV infection are available.<sup>97</sup>

Assessment of renal function should be made before initiation and during use of tenofovir, allowing avoidance, dose modification, or timely substitution of the drug when appropriate.<sup>27</sup>

#### HLA-B\*5701 Screening

The Prospective Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT) study demonstrated the clinical value of prospective HLA-B\*5701 screening to identify patients at risk of abacavir-associated hypersensitivity reaction (HSR).<sup>84</sup> Those screening negative for HLA-B\*5701 rarely develop immunologically confirmed abacavir HSR; approximately 50% of HLA-B\*5701-positive patients develop immunologically confirmed HSR when given abacavir. Thus, HLA-B\*5701-positive patients should not receive abacavir. When a patient screens negative for HLA-B\*5701, this should not replace careful follow-up because clinically diagnosed forms of abacavir HSR may still occur in such patients, albeit infrequently.

#### Therapeutic Drug Monitoring

The clinical role of therapeutic drug monitoring remains controversial, and no definitive data have emerged since the last edition of the guidelines on which to base a clear-cut recommendation.<sup>98-100</sup> When available with assays performed by a quality-assured

laboratory,<sup>101</sup> therapeutic drug monitoring of PIs and NNRTIs may be selectively useful in pregnant women,<sup>102,103</sup> children,<sup>104,105</sup> and patients with renal or liver failure<sup>106-108</sup>; to potentially minimize overexposure and adverse effects<sup>108-110</sup>; when managing potential drug-drug interactions<sup>99</sup>; or in virologic failure in the absence of resistance when adherence is thought to be excellent.

#### Recommendations

The goal of antiretroviral therapy is to reduce and maintain a plasma HIV-1 RNA level of less than 50 copies/mL, regardless of previous treatment experience. Plasma HIV-1 RNA levels should be monitored frequently when treatment is initiated or changed for virologic failure (eg, at 2, 4, 8, and every 4 weeks thereafter) (AIIa) until it reaches levels below the assay detection limits, and regularly thereafter (eg, 3-4 times per year [BIII]). Once the viral load is suppressed for an extended period and CD4 cell counts are stable at 350/μL or more, twice-yearly CD4 cell counts are reasonable (CIII).

Baseline genotypic testing for resistance should be performed in all treatment-naïve patients (AIIa and, in cases of confirmed virologic failure, AIa). Resistance testing should also be considered after a new regimen is introduced if the trajectory of HIV-1 RNA reduction is not optimal, as archived mutations may emerge (AII). Appropriate assessment of comorbid conditions and monitoring for toxicity should be performed before initiating treatment and during follow-up (eg, for hyperlipidemia, cardiovascular risk, renal function, and hepatic transaminases) and may be partly dependent on the regimen. When possible, patients should be screened for the HLA-B\*5701 haplotype if being considered for abacavir (AIa); those screening positive should not receive the drug (AIa). Those screening negative can generally take abacavir, but because rare cases of abacavir HSR may occur in such patients, clinical vigilance for suspected abacavir HSR remains appropriate (AIa).

Assessment of viral tropism is recommended prior to use of maraviroc (A1b). Therapeutic drug monitoring for PIs and first-generation NNRTIs is not recommended as part of routine care (CIII).

#### WHEN TO CHANGE AND WHAT TO CHANGE Changing for Reasons of Toxicity or Convenience

The principles for modifying a regimen successful in suppressing HIV have not changed.<sup>1</sup> Single-agent switches to decrease toxicity, avoid adverse drug interactions, or improve convenience and adherence are possible provided the potency of the regimen is maintained and subsequent drug interactions are managed appropriately.<sup>111-115</sup> Switching to PI/r monotherapy is not recommended, given the increased rates of low-level viremia,<sup>116</sup> unless other options are not available (BI). Caution must be taken in switching to nevirapine in women with CD4 cell counts of more than 250/μL and in men with CD4 cell counts of more than 400/μL, although studies have suggested that the risks of hypersensitivity and hepatotoxicity are lower than have been reported in antiretroviral-naïve individuals who start nevirapine with similar CD4 cell counts (BII).<sup>117,118</sup> Changes because of toxicity should not be made prematurely, as many early drug-related adverse effects subside with time. However, persistent adverse effects may compromise adherence and lead to resistance.

**Recommendations.** Replacing single agents to reduce toxicity or drug interactions or to improve convenience and adherence is acceptable provided the regimen potency is maintained and subsequent adverse drug interactions are avoided (AIIa). Prior treatment history and results of prior resistance testing should be reviewed. Close monitoring of HIV-1 RNA level after such a switch can help ensure that virologic suppression is maintained.

#### Changing for Virologic Failure

Viral load suppression to less than 50 copies/mL is now achievable in the ma-

majority of patients with virologic failure, even those with multidrug-resistant HIV.<sup>89,90,93,119-123</sup>

The selection of a new regimen should take into consideration history of drug exposure, current and prior genotypic or phenotypic resistance patterns, tolerability, other prescribed drugs with interaction potential, and reasons for failure and should include expert advice when possible. At least 2 (and ideally 3) fully active drugs should be included, and using drugs from at least 1 new class should be considered.

**First-Line Failure of NNRTI-Based Regimens.** There is no advantage to maintaining an NNRTI to which resistance has emerged. The failure of an agent should be recognized early and discontinued so that additional mutations to the NNRTI and dual-nRTI components do not emerge to compromise other compounds in the class.

First-line NNRTI failures are typically treated with 2 active nRTIs plus a PI/r. If such a regimen cannot be constructed, including etravirine or an agent in a new class, such as raltegravir or maraviroc (if virus is pure R5), can be considered if adequately supported by other active drugs in the regimen. Although etravirine retains activity in the setting of fewer than 3 NNRTI mutations and does not appear to be affected by K103N,<sup>124</sup> it will need to be supported by at least 1 fully active nRTI and a PI/r. Etravirine with 2 nRTIs alone is not recommended [BI].

**First-Line Failure of PI/r Regimens.** As with NNRTI-based regimens, failure should be detected early and mutations identified. For many patients, resistance to the PI may not have emerged, allowing the same drug or another PI/r to be used next. For virus with some degree of PI resistance, a PI/r with activity against resistant strains, such as lopinavir/r, darunavir/r, or tipranavir/r, should be considered. In this setting, darunavir/r is likely to be more active than lopinavir/r<sup>88</sup> and may be more tolerable than tipranavir/r. If not previously used, an NNRTI may be included, provided that drug interac-

tions are considered. Whenever possible, 2 fully active nRTIs should be included. If the combined potency is uncertain, including an agent from a new class, such as an integrase strand transfer inhibitor or a CCR5 antagonist (if R5 virus can be confirmed by tropism assay), should be considered.

With virologic failure of either an NNRTI- or a PI/r-based initial regimen, decisions should be individualized with respect to the number of new drugs and new drug classes used in the replacement combination. For early failures, strategic sequencing of PIs should be considered. For example, for a virus that is fully susceptible to all PIs, there is no virologic advantage to using darunavir/r or tipranavir/r over lopinavir/r or atazanavir/r.<sup>125</sup>

**Recommendations.** Virologic failure with an initial NNRTI- or PI-based regimen should be treated early with at least 2, and ideally 3, fully active drugs. For NNRTI failures, the new combination should include, if possible, an agent from a new class (A1a), most commonly a PI/r. With NNRTI failure, etravirine may be a useful component of a new regimen if there are fewer than 3 NNRTI-associated mutations, but it must be supported by a potent combination of other drugs that should include a PI/r (A1a). Depending on the drug resistance profile and options available, inclusion of an agent from another new drug class (raltegravir, an integrase inhibitor, or maraviroc, a CCR5 antagonist) should be considered (BIII).

#### **Multidrug (Including PI and NNRTI) Resistance**

In this setting, 3 active drugs, including new classes of agents whenever possible, should be used. Individuals with treatment failure and multidrug-resistant virus usually benefit from a PI/r with activity against resistant strains, such as darunavir/r or tipranavir/r.<sup>90,119</sup> Etravirine can be paired with darunavir/r but not tipranavir/r<sup>126</sup> and may be of value depending on the number of NNRTI mutations. One or more drugs drawn from newer classes should be

included, such as raltegravir or maraviroc (if R5 virus is confirmed).<sup>93,122,123</sup> Enfuvirtide may be of value despite the inconvenience of subcutaneous injection and the associated injection site reactions.<sup>127</sup> There is no convincing evidence for the use of 2 PI/rs (double PI boosting).<sup>128</sup> There is no new information on the role of continuing lamivudine (or emtricitabine) to maintain the M184V mutation to modulate viral fitness.

#### **Recently Approved Agents Particularly Useful in Multidrug-Experienced Patients**

**Raltegravir.** Patients with triple class-resistant HIV were randomized to receive raltegravir, 400 mg twice daily, or placebo in addition to optimized background therapy in 2 phase 3 trials (TABLE 4).<sup>122,123</sup> Human immunodeficiency virus 1 RNA levels of less than 50 copies/mL occurred in 65% of patients taking raltegravir and in 31% in the control groups. Virologic responses were greater in the subgroup of patients with lower baseline HIV-1 RNA levels, higher baseline CD4 cell counts, and who had more active agents in the optimized background therapy. There were non-statistically significantly increased numbers of cancers in patients randomized to receive active drug (relative risk at 48 weeks, 1.5; 95% CI, 0.5-6.3). It is unclear whether this imbalance is drug related or reflects anticipated complications in an advanced patient population. Raltegravir resistance remains under study but appears to involve a minimum of 2 mutations along 1 of 2 pathways of the integrase enzyme (Q148H/K/R or N155H).<sup>129</sup> Raltegravir is a potent agent for patients with multidrug resistance, but given its relatively low genetic barrier to resistance, it needs to be supported by other agents.

**Maraviroc.** Maraviroc was evaluated in triple class-experienced patients with R5 virus in 2 phase 3 studies (Table 4).<sup>93</sup> The mean HIV-1 RNA change from baseline in the placebo group was  $-0.78 \log_{10}$  copies/mL compared with  $-1.68 \log_{10}$  copies/mL with

once-daily maraviroc and  $-1.84 \log_{10}$  copies/mL with twice-daily maraviroc. Maraviroc has not been associated with an increased incidence of malignancy, but the question has been raised with another investigational drug in this class, vicriviroc, so careful phase 4 follow-up is ongoing. Resistance to maraviroc typically occurs through emergence of X4 or dual-/mixed-tropic virus preexistent in the viral population; a second mechanism involves mutations developing in gp120 of HIV-1 that permit the virus to use the CCR5 receptor in the presence of bound maraviroc.

**Etravirine.** Etravirine was evaluated in treatment-experienced patients in 2 parallel trials in which patients received etravirine, 200 mg twice daily, or matching placebo with daruna-

vir/r and optimized background therapy.<sup>120,121,130</sup> At 48 weeks, 65% of patients randomized to etravirine, compared with 39% to 40% randomized to placebo, had HIV-1 RNA levels of less than 50 copies/mL. More active agents in the optimized background therapy produced greater response rates. The presence of 3 or more NNRTI mutations was associated with a poor virologic response.<sup>124</sup> Most data for this agent have been derived from the trials in which it was combined with darunavir/r and other active agents, so its use in other combinations needs to be considered cautiously.

**Recommendations.** The treatment goal of suppression of HIV-1 RNA to less than 50 copies/mL in treatment-experienced patients, introduced in the last report,<sup>1</sup> has been strengthened by

recent advances (A1a). Regimens should include at least 2, and ideally 3, fully active agents (A1a), and at least 1 new class should be included (A1a). Expert advice should guide therapy for patients with multidrug resistance (BIII).

Ritonavir-boosted PIs with activity against resistant viruses (darunavir/r or tipranavir/r) often are the foundations of a new regimen. Adding raltegravir provides a potent agent from a new class. Raltegravir has a relatively low genetic barrier to resistance and, thus, needs to be protected by the addition of other agents to prevent virologic breakthrough (A1a).

Etravirine can be an important adjunct to a new regimen if no or only 1 or 2 NNRTI-associated resistance mutations are present (A1a), and it must be supported by a potent backbone (eg,

**Table 4.** Selected Trials of Newly Available Drugs in Antiretroviral-Experienced Patients

Class and Drug	Pivotal Trials in Multidrug-Resistant Patients	Entry Criteria	Randomization	Outcomes	Comments
Integrase inhibitor: raltegravir	BENCHMRK-1 (n = 352) <sup>122</sup> BENCHMRK-2 (n = 351) <sup>123</sup>	Multidrug resistance HIV RNA >1000 copies/mL Any CD4 cell count	Optimized background therapy + raltegravir or placebo (2:1 ratio)	HIV RNA <50 copies/mL at week 48: 60%-65% (raltegravir) vs 31%-34% (control) CD4 cell counts increased 98-120/ $\mu$ L (raltegravir) vs 40-49/ $\mu$ L (control)	Most frequent adverse events gastrointestinal; not increased vs placebo Relative risk of malignancy increased vs placebo; significance uncertain
CCR5 antagonist: maraviroc	Motivate-1 (n = 601) <sup>93</sup> Motivate-2 (n = 475) <sup>93</sup>	Multidrug resistance R5-tropic HIV RNA >5000 copies/mL Any CD4 cell count	Optimized background therapy + placebo or maraviroc once daily or maraviroc twice daily (1:2:2 ratio)	HIV RNA <50 copies/mL at week 48: 45.5% (maraviroc, once daily) and 43.2% (maraviroc, twice daily) vs 16.7% (control) CD4 cell counts increased 116/ $\mu$ L (maraviroc, once daily) and 124/ $\mu$ L (maraviroc, twice daily) vs 61/ $\mu$ L (control)	Need to perform tropism assay prior to use No increase in malignancy Most common adverse events: diarrhea, nausea, fatigue, and headache; similar to placebo
NNRTI: etravirine	DUET-1 (n = 612) <sup>120</sup> DUET-2 (n = 489) <sup>121</sup>	HIV RNA >5000 copies/mL $\geq 1$ NNRTI mutation $\geq 3$ PI mutations Any CD4 cell count	Ritonavir-boosted darunavir + optimized background therapy + etravirine or placebo	HIV RNA <50 copies/mL at week 48: 60%-61% (etravirine) vs 39%-41% (control) CD4 cell counts increased 94-103/ $\mu$ L (etravirine) vs 72-74/ $\mu$ L (control)	Fully active only if fewer than 3 resistance-associated mutations; activity not compromised by isolated K103N mutation Most data are based on combined use with darunavir

Abbreviation: HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor.

a boosted PI such as darunavir/r). Etravirine should not be used with tipranavir/r because of drug-drug interactions (AII).

For individuals with R5 virus, maraviroc can provide another active agent from a new class (AIIa). Tropism should be assessed when contemplating the use of maraviroc (AIIa). Concerns about the limited sensitivity of the tropism assays in excluding the presence of X4 virus are being addressed by the development and availability of more sensitive assays. Maraviroc is especially important to consider if the PI/r component of the regimen is compromised by PI resistance.

Despite its inconvenience, enfuvirtide remains an important agent for persons with multidrug-resistant virus, especially those with greater compromise of the PI component.

The nRTIs are often included in new regimens for highly treatment-experienced patients but typically provide only partial, adjunctive activity, given the frequent presence of drug class cross-resistance as a result of prior drug exposure. Their use as adjuncts is recommended in situations where residual antiretroviral activity is thought to be present and tolerance is good (BIIa).

### ANTIRETROVIRAL THERAPY IN SPECIAL POPULATIONS

In at least 3 circumstances, special consideration should be given to initiation of therapy.

#### HIV-Infected Persons With or at Risk of Specific Opportunistic Diseases and Coinfections

The presence of coinfections, or a high risk of certain opportunistic diseases, can provide a strong rationale for earlier initiation of therapy. Liver disease associated with HBV and HCV progresses more rapidly in HIV-1-coinfected populations than in those infected with HBV or HCV alone. Liver disease progression is slower in HIV/HCV-coinfected patients receiving effective antiretroviral therapy.<sup>131</sup> Therapy for HCV (eg, peginterferon alfa plus

ribavirin) is limited by toxicity, adherence challenges, and limited efficacy, particularly with HCV genotype 1 and 4 infection. Therefore, initiation of antiretroviral therapy, regardless of CD4 cell count in those coinfecting with HCV genotypes 1 and 4, in those with genotypes 2 or 3 who do not tolerate therapy, or in persons who do not clear virus despite a course of anti-HCV therapy might substantially reduce the rate of progression of liver disease.

In HBV coinfection, treatment for HIV should be considered at any CD4 cell count. A number of HIV drugs (tenofovir, emtricitabine, lamivudine) also are appropriate for HBV therapy and can be used in initial HIV regimens for HBV-coinfected patients.

The timing of antiretroviral therapy in those presenting with HIV-1 infection and an acute opportunistic infection was recently examined.<sup>132</sup> In HIV-1-infected persons presenting with a subset of treatable opportunistic infections, 6-month morbidity and mortality were reduced in those in whom antiretroviral therapy was initiated closer to the time of presentation than in those in whom therapy was delayed. This study excluded patients with tuberculosis; thus, the optimal approach to starting antiretroviral therapy in those with immunologically advanced HIV infection and tuberculosis remains an area of active investigation.

#### HIV-Associated Nephropathy

Abnormal kidney function is found in up to 30% of HIV-infected persons.<sup>133,134</sup> Proteinuric renal disease is more common in persons of African descent and persons with diabetes, hypertension, HCV infection, family history of kidney disease, CD4 cell count of less than 200/ $\mu$ L, or HIV-1 RNA level of more than 4000 copies/mL.<sup>27,133</sup> Antiretroviral therapy can improve renal function in HIVAN and may slow, if not stop, its progression.<sup>135-137</sup> Observational studies suggest that antiretroviral therapy may prevent HIVAN, as its prevalence has decreased in the era of highly active therapy.<sup>136</sup> Uncontrolled viral replication is associated with the

development of non-AIDS diseases, and renal disease is more prevalent in untreated HIV infection.<sup>27,35,36</sup>

#### Pregnant Women

Antiretroviral therapy for pregnant women with detectable HIV-1 RNA is indicated to improve the health of the mother and to prevent transmission of HIV-1 to the fetus or infant. Antiretroviral therapy should not be deferred in women in their first trimester of pregnancy if they are candidates for therapy, irrespective of pregnancy status. Complete recommendations for antiretroviral treatment during pregnancy should be used to guide therapy.<sup>53</sup>

#### Recommendations

Human immunodeficiency virus infection treatment may be considered at any CD4 cell count for persons coinfecting with HCV genotypes 1a, 1b, or 4 to slow the progression of liver disease (AIIa, AIIb). Therapy should also be considered for those with HCV genotypes 2 or 3 who do not clear virus with therapy or who cannot tolerate HCV treatment (AIIa, AIIb).

Active HBV coinfection should prompt consideration of initiation of antiretroviral therapy, irrespective of CD4 cell count, since earlier therapy might reduce the rate of liver disease progression (AIIa). Early antiretroviral therapy with at least 2 agents that are active against HBV will likely have a beneficial impact on liver disease and reduce the rate of evolution of drug-resistant HBV variants. Tenofovir and either emtricitabine or lamivudine are preferred for initial treatment of HBV in coinfection. The activity of entecavir against HIV has not yet been confirmed in clinical trials; therefore, it should not be substituted for an active nRTI for the treatment of HIV.<sup>138</sup>

Persons with HIVAN should begin antiretroviral therapy (AIIa, AIIb) as soon as renal disease is diagnosed.<sup>27</sup> Drugs with potential nephrotoxicity should be avoided in persons with renal abnormalities, if possible. When potentially nephrotoxic drugs like atazanavir (nephrolithiasis) and tenofovir

(renal tubular disorders) are used, renal function should be monitored closely.

## CONCLUSIONS

The 21 years since zidovudine was approved for the treatment of HIV infection have witnessed remarkable advances in the understanding of disease pathogenesis, translation of that knowledge into practical therapeutics, continued discovery of complications or disease states associated with HIV or its treatment that increase the complexity of management, and a dynamic drug development process that has led to the current availability of more than 30 individual drugs and fixed-dose combinations to treat HIV infection.

Despite these advances, disease management remains challenged by toxicities, maintenance of adherence, clinical manifestations related to both the drugs and the HIV infection itself, and the threat of drug resistance. Sustainability and expansion of the progress achieved will depend on maintaining a robust drug development pipeline and the ability to deliver effective therapy and monitoring tools to the world's affected populations. With creativity and political will, the progress and individualized approach to antiretroviral therapy evident in the developed world can be adapted to the public health approach in the developing world, where 90% of the world's HIV-infected population lives.

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*Administrative, technical, or material support:* Hammer, Schooley, Jacobsen, Yeni.

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**Financial Disclosures:** Dr Hammer reports that he has served as a scientific advisor to Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Pfizer, Progenics, Schering, Shire, TaiMed Biologics, and Tibotec-Virco; has received a clinical trial research contract from Merck; and has served on a data and safety monitoring board for Bristol-Myers Squibb. Dr Eron reports that he was the principal investigator on research grants to University of North Carolina from Boehringer Ingelheim, GlaxoSmithKline, Merck, and Panacos; has served as a consultant to Avexa, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Monogram, Panacos, Pfizer, Tibotec, and Tobira; and was on the speakers' bureaus for or received honorarium from Bristol-Myers Squibb, Merck, Roche, and Tibotec. Dr Reiss reports that he has served on advisory boards and/or speakers' bureaus for and/or received research grants from Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Science, GlaxoSmithKline, Hoffmann, LaRoche, Merck, Pfizer, Theratechnologies, and Tibotec. Dr Schooley reports that he has served as a consultant to Achillion, Anadys, Ardea, Gilead, GlaxoSmithKline, ImQuest, Inhibitex, Koronis, Merck, Monogram, Myriad, Pfizer, TaiMed, Tanox, Tibotec, Tobira, and Vertex; has received grant support from Merck and Chimerix; and has had stock options for Achillion and Monogram. Dr Thompson reports that she has received research grants for AIDS Research Consortium of Atlanta from Abbott, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Koronis, Merck, Panacos, Pfizer, Progenics, Roche, Serono, TaiMed, Theratechnologies, and Tibotec; has spoken at events sponsored by GlaxoSmithKline and Serono; and has served as a consultant to or was on the scientific advisory boards for GlaxoSmithKline, Gilead, Panacos, Pfizer, Progenics, Serono, and Tibotec. Dr Walmsley reports that she has served on advisory boards and/or speakers' bureaus for Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Roche, and Tibotec. Dr Cahn reports that he has received fees for consultancy, speaking engagements, scientific advisory board membership, and/or research grants from Abbott, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann LaRoche, Merck, Pfizer, Pharmasset, Schering-Plough, and Tibotec. Dr Fischl reports that she has received research grants from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Progenics Pharmaceuticals, and Cytheris and has served on advisory boards for Merck and Progenics Pharmaceuticals. Dr Gatell reports that he has received honoraria for speaking or participating in advisory boards or research grants from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Janssen, MSD, Pfizer, Roche, Tibotec, and Tobira. Dr Hirsch reports that he has served on data safety monitoring boards for Merck

and TaiMed Biologics. Dr Montaner reports that he has received grants from, served an advisor to, or spoken at events sponsored by Abbott, Argos Therapeutics, Bioject Inc, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Janssen-Ortho, Merck Frosst, Panacos, Pfizer, Schering, Serono Inc, TheraTechnologies, Tibotec, and Trimeris. Dr Richman reports that he has served as a consultant to Anadys Pharmaceuticals, Biota, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Idenix, Koronis Pharmaceuticals, Merck, Monogram Biosciences, Pfizer, Roche, and Tobira. Dr Yeni reports that he has received grants and research support from Bristol-Myers Squibb, GlaxoSmithKline, Merck, Roche, and Tibotec and has served as a consultant to Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, and Tibotec. Dr Volberding reports that he has served on scientific advisory boards for Bristol-Myers Squibb, Gilead, Merck, Pfizer, and Schering; has participated as a member of an endpoint adjudication committee of Schering for an ongoing clinical trial; has provided expert testimony in a lawsuit against Abbott Laboratories; and has received an unrestricted educational grant from GlaxoSmithKline-Italy. The IAS-USA has received grants for selected continuing medical education activities that are pooled (ie, no single company supports any single effort) from Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Roche, and Tibotec. No other disclosures were reported.

**Funding/Support:** This work was funded by the IAS-USA. Panel members serve in volunteer capacities (ie, are not compensated). No private sector or government funding contributed to this work.

**Role of the Sponsor:** The IAS-USA determined the need for updated recommendations, selected the panel members, and provided administrative oversight and financial support.

**Additional Contributions:** We thank Brian G. Gazzard, MD, FRCP, Chelsea and Westminster Hospital, London, England; Michael S. Saag, MD, University of Alabama at Birmingham; Mauro Schechter, MD, PhD, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; and Charles C. J. Carpenter, MD, Brown University School of Medicine, Providence, Rhode Island; for helpful comments; and Michelle Tayag, BS, who was compensated as an employee of the IAS-USA, for administrative support.

## REFERENCES

1. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society—USA panel. *JAMA*. 2006;296(7):827-843.
2. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006;367(9513):817-824.
3. Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996: recommendations of an international panel. *JAMA*. 1996;276(2):146-154.
4. 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(3):251-260.
5. Dubé MP, Komarow L, Mulligan K, et al. Long-term body fat outcomes in antiretroviral-naïve participants randomized to nelfinavir or efavirenz or both plus dual nucleosides: dual x-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. *J Acquir Immune Defic Syndr*. 2007;45(5):508-514.
6. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treat-

- ment of HIV infection in adults: the first 4 years. *AIDS*. 2007;21(10):1273-1281.
7. Podzamczar D, Ferrer E, Sanchez P, et al. Less lipotrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. *J Acquir Immune Defic Syndr*. 2007;44(2):139-147.
  8. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new onset diabetes mellitus in HIV-infected patients: the D:A:D study. *Diabetes Care*. 2008;31(6):1224-1229.
  9. Riedel DJ, Gebo KA, Moore RD, Lucas GM. A ten-year analysis of the incidence and risk factors for acute pancreatitis requiring hospitalization in an urban HIV clinical cohort. *AIDS Patient Care STDS*. 2008;22(2):113-121.
  10. Smith K, Fine D, Patel P, et al. Efficacy and safety of abacavir/lamivudine compared to tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir through 48 weeks in the HEAT study. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 774.
  11. Wood E, Hogg RS, Yip B, Moore D, Harrigan PR, Montaner JS. Superior virological response to boosted protease inhibitor-based highly active antiretroviral therapy in an observational treatment programme. *HIV Med*. 2007;8(2):80-85.
  12. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120(8):713-719.
  13. Eron J Jr, Yeni P, Gathe J Jr, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomized non-inferiority trial. *Lancet*. 2006;368(9534):476-482.
  14. Kempf DJ, King MS, Bernstein B, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. *J Infect Dis*. 2004;189(1):51-60.
  15. Palella FJ, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006;43(1):27-34.
  16. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS*. 2007;21(9):1185-1197.
  17. Smit C, Geskus R, Walker S, et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. *AIDS*. 2006;20(5):741-749.
  18. Reisler RB, Han C, Burman WJ, Tedaldi EM, Neaton JD. Grade 4 events are as important as AIDS events in the era of HAART. *J Acquir Immune Defic Syndr*. 2003;34(4):379-386.
  19. Neaton J, Grund B. Earlier initiation of antiretroviral therapy in treatment-naive patients: implications of results of treatment interruption trials. *Curr Opin HIV/AIDS*. 2008;3:112-117.
  20. Lau B, Gange SJ, Moore RD. Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4<sup>+</sup> counts greater than 200 cells/mm<sup>3</sup>. *J Acquir Immune Defic Syndr*. 2007;44(2):179-187.
  21. Phillips A. Morbidity and mortality in the HAART era. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 8.
  22. Grulich AE, Van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007;370(9581):59-67.
  23. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS*. 2008;22(4):489-496.
  24. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med*. 2008;148(10):728-736.
  25. Friis-Møller N, Reiss P, Sabin CA, et al; D:A:D Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735.
  26. Weber R, Sabin CA, Friis-Møller N. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D Study. *Arch Intern Med*. 2006;166(15):1632-1641.
  27. 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(11):1559-1585.
  28. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. Racial differences in end-stage renal disease rates in HIV infection versus diabetes. *J Am Soc Nephrol*. 2007;18(11):2968-2974.
  29. Lodwick R, Porter K, Sabin C, et al. Age- and sex-specific death rates in ART-naive patients with CD4 count above 350 cells/mm<sup>3</sup> compared with the general population. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 141.
  30. Bruyand M, Thiebaut R, Lawson-Ayayi S, et al. Immunodeficiency and risk of AIDS-defining and non-AIDS-defining cancers: ANRS C03 Aquitaine Cohort, 1998 to 2006. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 15.
  31. Kuller L; SMART Study Group. Elevated levels of interleukin-6 and D-dimer are associated with an increased risk of death in patients with HIV. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 139.
  32. Neal B. Quantifying the importance of interleukin-6 for coronary heart disease. *PLoS Med*. 2008;5(4):e84.
  33. Danesh J, Kaptoge S, Mann AG, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and systematic review. *PLoS Med*. 2008;5(4):e78.
  34. Ledwen C, Chene G, Morlat P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm<sup>3</sup> on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr*. 2007;46(1):72-77.
  35. Lundgren JD, Babiker A, El-Sadr W; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Inferior clinical outcome of the CD4<sup>+</sup> count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4<sup>+</sup> cell counts and HIV-RNA levels during follow-up. *J Infect Dis*. 2008;197(8):1145-1155.
  36. El-Sadr WM, Lundgren JD, Neaton JD, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4<sup>+</sup> count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.
  37. El-Sadr W; SMART Study Group. Re-initiation of ART in the CD4-guided ART interruption group in the SMART study lowers risk of opportunistic disease or death. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 36.
  38. Emery S, Neuhaus JA, Phillips AN, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis*. 2008;197(8):1133-1144.
  39. 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(9327):119-129.
  40. Jaén A, Esteve A, Miro JM, et al. Determinants of HIV progression and assessment of the optimal time to initiate highly active antiretroviral therapy: PISCIS Cohort (Spain). *J Acquir Immune Defic Syndr*. 2008;47(2):212-220.
  41. Moore RD, Keruly JC. CD4<sup>+</sup> cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446.
  42. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm<sup>3</sup> or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm<sup>3</sup> or greater. *J Acquir Immune Defic Syndr*. 2007;45(2):183-192.
  43. Phillips AN, Gazzard BG, Clumeck N, Losso MH, Lundgren JD. When should antiretroviral therapy for HIV be started? *BMJ*. 2007;334(7584):76-78.
  44. Phillips AN, Gazzard B, Gilson R, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count. *AIDS*. 2007;21(13):1717-1721.
  45. Braithwaite RS, Roberts MC, Chang CC, et al. Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy: a decision model. *Ann Intern Med*. 2008;148(3):178-185.
  46. Hill A, Miralles D, Vangeneuden T, Lefebvre E. Should we now adopt the HIV-RNA <50 copy endpoint for clinical trials of antiretroviral-experienced as well as naive patients? *AIDS*. 2007;21(12):1651-1653.
  47. Lichtenstein KA, Armon C, Buchacz K, et al. Initiation of antiretroviral therapy at CD4 cell counts >=350 cells/mm<sup>3</sup> does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency. *J Acquir Immune Defic Syndr*. 2008;47(1):27-35.
  48. Palella FJ, Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4<sup>+</sup> cell strata. *Ann Intern Med*. 2003;138(8):620-626.
  49. Opravil M, Ledergerber B, Furrer H, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count >350x10<sup>6</sup>/L. *AIDS*. 2002;16(10):1371-1381.
  50. Kaplan JE, Hanson DL, Cohn DL, et al. When to begin highly active antiretroviral therapy? evidence supporting initiation of therapy at CD4<sup>+</sup> lymphocyte counts <350 cells/μL. *Clin Infect Dis*. 2003;37(7):951-958.
  51. Mauskopf J, Kitahata M, Kauf T, Richter A, Tolson J. HIV antiretroviral treatment: early versus later. *J Acquir Immune Defic Syndr*. 2005;39(5):562-569.
  52. Sterling TR, Chaisson RE, Keruly J, Moore RD. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. *J Infect Dis*. 2003;188(11):1659-1665.
  53. Perinatal HIV Guidelines Working Group. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States—November 2, 2007. <http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed April 13, 2008.
  54. Quinn TC, Wawer MJ, Sewankambo N, et al; Rakai Project Study Group. Viral load and heterosexual trans-

- mission of human immunodeficiency virus type 1. *N Engl J Med*. 2000;342(13):921-929.
55. Castilla J, del Romero J, Hernando V, Marinovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr*. 2005;40(1):96-101.
56. Kayitenkore K, Bekan B, Rufagari J, et al. The impact of ART on HIV transmission among HIV serodiscordant couples. Presented at: 16th International AIDS Conference; August 13-18, 2006; Toronto, Ontario, Canada. Abstract MOKC101.
57. Wheeler W, Mahle K, Bodnar U, Kline R, Hall I, McKenna M. Antiretroviral drug-resistance mutations and subtypes in drug-naive persons newly diagnosed with HIV-1 infection, US, March 2003 to October 2006. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 648.
58. SPREAD Programme. Transmission of drug-resistant HIV-1 in Europe remains limited to single classes. *AIDS*. 2008;22(5):625-635.
59. Ridder SA, Haubrich RH, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106.
60. Haubrich RH, Ridder S, DiRienzo G, et al. Metabolic outcomes of ACTG 5142: a prospective, randomized, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 38.
61. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes—a 96-week analysis. *J Acquir Immune Defic Syndr*. 2006;43(5):535-540.
62. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr*. 2008;47(1):74-78.
63. 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(2):191-201.
64. Gulick RM, Ribaldo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA*. 2006;296(7):769-781.
65. Ribaldo HJ, Kuritzkes DR, Lalama CM, et al. Efavirenz-based regimens in treatment-naive patients with a range of pretreatment HIV-1 RNA levels and CD4 cell counts. *J Infect Dis*. 2008;197(7):1006-1010.
66. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Efficacy and safety of once-daily atazanavir/ritonavir compared to twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine in ARV-naive HIV-1-infected subjects: the CASTLE study, 48-week results. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 37.
67. Walmsley S, Ruxrungtham K, Slim J, et al. Saquinavir/r (SQV/r) BiD versus lopinavir/r (LPV/r) BiD, plus emtricitabine/tenofovir (FTC/TDF) QD as initial therapy in HIV-1 infected patients: the GEMINI study. Presented at: 11th Conference on Retroviruses and Opportunistic Infections; October 24-27, 2007; Madrid, Spain. Abstract PS1/4.
68. Clumeck N, van Lunzen J, Chiliade P, et al. ARTEMIS: efficacy and safety of lopinavir (BID vs QD) and darunavir (QD) in antiretroviral-naive patients. Presented at: 11th European AIDS Conference; October 24-27, 2007; Madrid, Spain. Abstract LBPS7/5.
69. Gathe J, Da Silva B, Loutfy M, et al. Primary efficacy results at week 48: phase 3 randomized, open-label study of lopinavir/ritonavir tablets once daily vs twice daily, co-administered with tenofovir DF + emtricitabine in ARV-naive HIV-1-infected subjects. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 775.
70. Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. 2008;47(2):161-167.
71. Smith K, Weinberg W, DeJesus E, et al. Once-daily ritonavir (100 mg) boosting of fosamprenavir (FPV/r) or atazanavir (ATZ/r) with tenofovir(TDF)/emtricitabine(FTC) in antiretroviral-naive HIV-infected patients: 48-week safety/efficacy results from COL103952 (ALERT). Presented at: 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract WEPEB023.
72. Parsonage MJ, Wilkins EG, Snowden N, Issa BG, Savage MW. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. *HIV Med*. 2005;6(5):341-346.
73. Badiou S, de Boever CM, Terrier N, Baillat V, Cristol JP, Reynes J. Is tenofovir involved in hypophosphatemia and decrease of tubular phosphate reabsorption in HIV-positive adults? *J Infect*. 2006;52(5):335-338.
74. Sabin C, Worm SW, Weber R, et al; D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426.
75. Stein JH, Currier JS. Risk of myocardial infarction and nucleoside analogues. *Lancet*. 2008;371(9622):1391-1392.
76. Delfrayssy JF, Flandre P, Delaunay C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. *AIDS*. 2008;22(3):385-393.
77. 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(1):73-78.
78. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J Acquir Immune Defic Syndr*. 2006;43(5):509-515.
79. Steigbigel R, Kumar P, Eron J, et al. Results of BENCHMRK-2, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 105bLB.
80. Cooper D, Gatell J, Rockstroh J, et al. Results of BENCHMRK-1, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 105aLB.
81. Markowitz M, Nguyen BY, Gotuzzo E, et al. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr*. 2007;46(2):125-133.
82. Saag M, Iye P, Heera J, et al. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine [ZDV]/lamivudine [3TC]), for the treatment of antiretroviral naive subjects infected with R5 HIV-1: week 48 results of the MERIT study. Presented at: 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract WESS104.
83. Department of Health and Human Services. AIDS Clinical Trials Group Web site. [http://www.aactg.org/\\_\\*\\_news\\_results.asp\\*\\_](http://www.aactg.org/_*_news_results.asp*_). Accessed March 31, 2008.
84. Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
85. 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(1):99-102.
86. Luber AD, Brower R, Kim D, Silverman R, Peloquin CA, Frank I. Steady-state pharmacokinetics of once-daily fosamprenavir/ritonavir and atazanavir/ritonavir alone and in combination with 20 mg omeprazole in healthy volunteers. *HIV Med*. 2007;8(7):457-464.
87. Bristol-Myers Squibb. Reyataz [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2007.
88. Madruga JV, Berger D, McMurchie M, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomized controlled phase III trial. *Lancet*. 2007;370(9581):49-58.
89. Madruga JV, Cahn P, Grinsztejn B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2007;370(9581):29-38.
90. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet*. 2007;369(9568):1169-1178.
91. Lazzarin A, Campbell T, Clotet B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2007;370(9581):39-48.
92. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society—USA. *Clin Infect Dis*. 2008;47(2):266-285.
93. Hardy D, Reynes J, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in treatment-experienced patients infected with CCR5-tropic HIV-1: 48-week combined analysis of the MOTIVATE studies. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 792.
94. Mayer H, van der Ryst E, Saag M, et al. Safety and efficacy of maraviroc (MVC), a novel CCR5 antagonist, when used in combination with optimized background therapy (OBT) for the treatment of antiretroviral-experienced subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial. Presented at: 16th International AIDS Conference; August 13-18, 2006; Toronto, Ontario, Canada. Abstract ThLB0215.
95. Skrabal K, Low AJ, Dong W, et al. Determining human immunodeficiency virus coreceptor use in a clinical setting: degree of correlation between two phenotypic assays and a bioinformatic model. *J Clin Microbiol*. 2007;45(2):279-284.
96. Law MG, Friis-Moller N, El-Sadr WM, et al. The use of the Framingham equation to predict myocar-

- dial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med.* 2006;7(4):218-230.
97. Lundgren JD, Battegay M, Behrens G, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med.* 2008;9(2):72-81.
98. Khoo SH, Lloyd J, Dalton M, et al. Pharmacologic optimization of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (POPIN)—a randomized controlled trial of therapeutic drug monitoring and adherence support. *J Acquir Immune Defic Syndr.* 2006;41(4):461-467.
99. Park-Wyllie LY, Levine MA, Holbrook A, et al. Outcomes of dosage adjustments used to manage antiretroviral drug interactions. *Clin Infect Dis.* 2007;45(7):933-936.
100. van Luin MK, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS.* 2008;3(3):266-271.
101. Holland DT, DiFrancesco R, Stone J, et al. Quality assurance program for clinical measurement of antiretrovirals: AIDS clinical trials group proficiency testing program for pediatric and adult pharmacology laboratories. *Antimicrob Agents Chemother.* 2004;48(3):824-831.
102. Lyons F, Lechelt M, de Ruiter A. Steady-state lopinavir levels in third trimester of pregnancy. *AIDS.* 2007;21(8):1053-1054.
103. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS.* 2007;21(18):2409-2415.
104. Rosso R, Biagio A, Dentone C, et al. Lopinavir/ritonavir exposure in treatment-naïve HIV-infected children following twice or once daily administration. *J Antimicrob Chemother.* 2006;57(6):1168-1171.
105. von Hentig N, Koenigs C, Elanjikal S, et al. Need for therapeutic drug monitoring in HIV-1 infected children receiving efavirenz doses according to international guidelines. *Eur J Med Res.* 2006;11(9):377-380.
106. Seminari E, Gentilini M, De Bona A, et al. Liver cirrhosis but not chronic hepatitis is associated to higher amprenavir plasma levels in patients treated with fosamprenavir/ritonavir. 6th International Workshop on Clinical Pharmacology of HIV Therapy; April 26-27, 2005; Quebec City, Quebec, Canada. Abstract 66.
107. Kearney B, Liaw S, Yale K, et al. Pharmacokinetics following single-dose administration of tenofovir DF in patients with renal impairment. Presented at: 6th International Congress on Drug Therapy in HIV Infection; November 17-21, 2002; Glasgow, Scotland. Abstract 4.
108. Barreiro P, Rodriguez NS, Labarga P, et al. Influence of liver fibrosis stage on plasma levels of antiretroviral drugs in HIV-infected patients with chronic hepatitis C. *J Infect Dis.* 2007;195(7):973-979.
109. Lötsch J, Harder S, Sturmer M, et al. Association of saquinavir plasma concentrations with side effects but not with antiretroviral outcome in patients infected with protease inhibitor-susceptible human immunodeficiency virus type 1. *Antimicrob Agents Chemother.* 2007;51(9):3264-3272.
110. Cleijnsen RM, Van de Ende ME, Kroon FP, et al. Therapeutic drug monitoring of the HIV protease inhibitor atazanavir in clinical practice. *J Antimicrob Chemother.* 2007;60(4):897-900.
111. Martin A, Smith DE, Carr A, et al. Reversibility of lipotrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX extension study. *AIDS.* 2004;18(7):1029-1036.
112. Moyle GJ, Baldwin C, Langroudi B, Mandalia S, Gazzard BG. A 48-week, randomized, open-label comparison of three abacavir-based substitution approaches in the management of dyslipidemia and peripheral lipotrophy. *J Acquir Immune Defic Syndr.* 2003;33(1):22-28.
113. Ward DJ, Curtin JM. Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in lipid profiles. *AIDS Patient Care STDS.* 2006;20(8):542-548.
114. Alvarez D, Dieterich DT, Brau N, Moores L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat.* 2006;13(10):683-689.
115. Harris M, Larsen G, Montaner J. Outcomes of patients switched from enfuvirtide to raltegravir within a virologically suppressive regimen. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 799.
116. Cameron W, Da Silva BA, Arribas JR, et al. A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy D. *J Infect Dis.* 2008;198:234-240.
117. Mocroft A, Staszewski S, Weber R, et al. Risk of discontinuation of nevirapine due to toxicities in antiretroviral-naïve and -experienced HIV-infected patients with high and low CD4<sup>+</sup> T-cell counts. *Antivir Ther.* 2007;12(3):325-333.
118. De Lazzari E, Leon A, Arnaiz JA, et al. Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts. *HIV Med.* 2008;9(4):221-226.
119. Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimized background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in Multi-drug Resistant Patients With Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet.* 2006;368(9534):466-475.
120. Haubrich R, Cahn P, Grinsztejn B, et al. DUET-1: week-48 results of a phase III randomized double-blind trial to evaluate the efficacy and safety of TMC125 vs placebo in 612 treatment-experienced HIV-1-infected patients. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 790.
121. Johnson M, Campbell T, Clotet B, et al. DUET-2: 48-week results of a phase III randomized double-blind trial to evaluate the efficacy and safety of TMC125 vs placebo in 591 treatment-experienced HIV-1-infected patients. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 791.
122. Cooper D, Gatell J, Rockstroh J, et al. 48-week results from BENCHMRK-1, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV-1. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 788.
123. Steigbigel R, Kumar P, Eron J, et al. 48-Week results from BENCHMRK-2, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 789.
124. Vingerhoets J, Buelens A, Peeters M, et al. Impact of baseline NNRTI mutations on the virological response to TMC125 in the phase III clinical trials DUET-1 and DUET-2. *Antivir Ther.* 2007;12(suppl):S34.
125. Walmsley SL, Cotte L, Rusconi S, et al. Treatment response to ritonavir-boosted tipranavir versus ritonavir-boosted lopinavir in HIV-1 patients with higher lopinavir mutation scores. *AIDS.* 2007;21(16):2245-2248.
126. Scholler M, Kraft M, Hoetelmans R, et al. Significant decrease in TMC125 exposures when co-administered with tipranavir boosted with ritonavir in healthy subjects. Presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 583.
127. Reynes J, Arasteh K, Clotet B, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS.* 2007;21(8):533-543.
128. Walmsley SL, Katlama C, Lazzarin A, et al. Pharmacokinetics, safety, and efficacy of tipranavir boosted with ritonavir alone or in combination with other boosted protease inhibitors as part of optimized combination antiretroviral therapy in highly treatment-experienced patients (BI Study 1182.51). *J Acquir Immune Defic Syndr.* 2008;47(4):429-440.
129. Hazuda DJ, Miller MD, Nguyen BY, Zhao J; P005 Study Team. Resistance to the HIV-integrase inhibitor raltegravir: analysis of protocol 005, a phase II study in patients with triple-class resistant HIV-1 infection. *Antivir Ther.* 2007;12(suppl):S10.
130. Trottier B, Johnson M, Katlama C, et al. Pooled 48-week analysis of DUET-1 and DUET-2: durable efficacy and safety results of etravirine (TMC125; ETR) in treatment-experienced HIV-infected patients. Presented at: 17th Annual Canadian Conference on HIV/AIDS Research; April 24-27, 2008; Montreal, Quebec, Canada. Abstract P167.
131. Sherman K, Andersen J, Butt A, et al. Sustained long-term antiviral maintenance with pegylated interferon in HCV/HIV-co-infected patients: early viral response and effect on fibrosis in treated and control subjects. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 59.
132. Zolopa A, Andersen J, Komarow L, et al. Immediate vs deferred ART in the setting of acute AIDS-related opportunistic infection: final results of a randomized strategy trial, ACTG A5164. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 142.
133. Szczec LA, Gange SJ, Van Der Horst C, et al. Predictors of proteinuria and renal failure among women with HIV infection. *Kidney Int.* 2002;61(1):195-202.
134. Gupta SK, Mamlin BW, Johnson CS, Dollins MD, Topf JM, Dube MP. Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. *Clin Nephrol.* 2004;61(1):1-6.
135. Szczec LA, Edwards LJ, Van Der Horst C, Bartlett JA, Heald AE, Svetkey LP. Protease inhibitors are associated with a slowed progression of HIV-related renal diseases. *Clin Nephrol.* 2002;57(5):336-341.
136. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS.* 2004;18(3):541-546.
137. Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med.* 2001;344(26):1979-1984.
138. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med.* 2007;356(25):2614-2621.