

Perspective

# Strategic Approaches to Antiretroviral Treatment

*A useful clinical framework for decision making in antiretroviral treatment is to consider treatment options and goals at 4 decision points: initial therapy, early treatment failure, late treatment failure with high CD4+ cell count, and late treatment failure with low CD4+ cell count. Basic principles appropriate to these decision points are discussed. For initial treatment, the goal is to suppress viral replication for as long as possible. In early failure, the aim is to achieve resuppression of viral replication. For late treatment failure in patients with high CD4+ cell counts with limited treatment options, a reasonable approach is to be cautious in making treatment changes, since sustained incomplete suppression is not associated with immunologic collapse. In patients with late treatment failure and lower CD4+ cell counts, a reasonable strategy is to maintain some form of antiretroviral therapy until new drug classes become available. These basic approaches are reviewed in this article, with findings reported at the recent 10th Conference on Retroviruses and Opportunistic Infections discussed in light of this strategic framework. This article summarizes a presentation given by Diane V. Havlir, MD, at the March 2003 International AIDS Society–USA course in Los Angeles.*

Selection of an antiretroviral treatment regimen requires consideration of a variety of factors, including potency, safety, and tolerability of regimens; resistance patterns; and the clinical and immunologic condition of the patient. A useful clinical framework for decision making is to consider treatment options and goals at 4 decision points: initial therapy; early treatment failure, with treatment failure defined as loss of viral suppression; late treatment failure with high CD4+ cell count; and late treatment failure with low CD4+ cell count (see Table 1). Decisions and recommendations regarding which regimens to use at these points should be continuously reexamined on the basis of emerging data. Several studies reported at the recent 10th Conference on Retroviruses and Opportunistic Infections (CROI) add to the body of data that needs to be considered in formulating optimal treatment strategies.

## Initial Treatment

The guiding principle for selection of an initial antiretroviral regimen may be best formulated as *choose a regimen to avoid treatment failure*. Thus, the initial

regimen should provide optimal antiviral potency, facilitate adherence, and minimize toxicity. Currently, optimal potency is regarded as reduction in plasma HIV-1 RNA levels to less than 50 copies/mL. Although this cut-off point initially reflected assay detection limits, it has since been found that reaching this level has real biologic significance in terms of producing durable suppression.

Among the many possible combinations of antiretroviral drugs, Dr Havlir noted that in her opinion a few have emerged as leading candidates for initial therapy based on available data. For

triple-drug regimens, these include efavirenz or lopinavir/ritonavir plus a backbone of lamivudine with either zidovudine or tenofovir. Although some 4-drug regimens may achieve optimal viral suppression more rapidly than do 3-drug regimens, the overall superiority of a 4-drug approach remains unproven, and the associated increase in toxicity is an important consideration. Although potent antiretroviral therapy has traditionally involved 3-drug regimens, some current or future 2-drug combinations may achieve optimal viral suppression. One ongoing large comparative trial (ACTG 5142) is evaluating potency, toxicity, and tolerability of initial treatment with an efavirenz-based 3-drug regimen, a lopinavir/ritonavir-based 3-drug regimen, and the dual combination of efavirenz plus lopinavir/ritonavir.

The 96-week follow-up of a tenofovir trial reported at the 10th CROI provides some important information regarding use of tenofovir-including regimens in initial therapy. Two primary concerns with using tenofovir in an initial regimen were the modest CD4+ cell count increases observed with single-drug treatment in initial studies in treatment-experienced patients and the adverse effects that occurred when the drug was used in long-term combination treat-

**Table 1.** Treatment Principles at Major Decision Points in Antiretroviral Therapy

Decision Point	Treatment Principle
Initial Treatment	Choose a regimen to avoid treatment failure and suppress viral replication for as long as possible
Early Treatment Failure	Treat aggressively to achieve resuppression of viral replication
Late Treatment Failure*, High CD4+ Cell Count	Continue treatment with monitoring
Late Treatment Failure, Low CD4+ Cell Count	Maintain antiretroviral therapy until new drugs become available

\*No suppressive antiretroviral regimen available

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ment. In the trial reported by Staszewski et al, 600 treatment-naïve patients received efavirenz/lamivudine plus either tenofovir once daily or stavudine twice daily for 144 weeks. Data at 96 weeks indicate comparable virologic response to the 2 regimens, with intent-to-treat analysis showing plasma HIV-1 RNA reduction to less than 50 copies/mL in 78% of the tenofovir arm and 74% of the stavudine arm. CD4+ cell count responses were robust in both arms, with increases of 261 and 266 cells/ $\mu$ L for the tenofovir and stavudine arms, respectively. A lower frequency of toxicities associated with mitochondrial dysfunction was observed in the tenofovir arm, with peripheral neuritis/neuropathy occurring in 3% of patients on tenofovir versus 10% of patients on stavudine ( $P < .001$ ), investigator-defined lipodystrophy in 1% versus 12% ( $P < .001$ ), and investigator-defined lactic acidosis in 0% versus 1%. No pancreatitis was observed. The relative risk of these combined adverse events was 5.5 (95% confidence interval, 3.0-10.3) in the stavudine arm. Total limb fat as measured by dual x-ray absorptiometry was significantly greater in the tenofovir group at 96 weeks; although no longitudinal analysis was performed, these data suggest less peripheral fat loss in the tenofovir group. Adverse lipid changes were also less common in tenofovir-treated patients. Increases from baseline in fasting triglyceride and total cholesterol levels were lower at 96 weeks in the tenofovir arm than in the stavudine arm (5 mg/dL vs 103 mg/dL and 30 mg/dL vs 51 mg/dL, respectively; both  $P < .001$ ). New lipid-lowering therapy was prescribed in fewer patients in the tenofovir arm than in the stavudine arm (2% vs 10%,  $P < .001$ ). The findings in this trial thus alleviate some of the concerns regarding up-front use of tenofovir on the basis of antiviral potency and reductions in some important long-term toxicities compared with the other regimen in the study.

The 48-week findings of a large international study presented at the 10th CROI also highlight the need to take tolerability and toxicity into account in overall assessment of antiviral effectiveness (van Leth, 2003). In this trial, 1216 treatment-naïve patients received a dual nucleoside reverse tran-

scriptase inhibitor (nRTI) backbone plus efavirenz, plus nevirapine once daily, plus nevirapine twice daily, or plus efavirenz and nevirapine. Antiretroviral potency was not higher in the patients receiving both efavirenz and nevirapine and was comparable across the 4 arms in terms of proportions of patients achieving viral suppression. Toxicity and treatment discontinuations were significantly higher in the nevirapine plus efavirenz arm, resulting in a significantly higher treatment failure rate in this arm compared with the other 3 arms. Liver-associated adverse events were also higher in the nevirapine once-daily (13.2%) and twice-daily (7.8%) arms compared with the efavirenz arm (4.5%). Reduced tolerability or increased toxicity may require withdrawal of a drug or regimen, and the ability to remain on suppressive treatment is an important measure of the effectiveness of the treatment.

### Early Treatment Failure

Precisely what level of viral rebound should be considered indicative of virologic failure meriting a treatment switch appears to differ among practitioners, with many feeling that a plasma HIV-1 RNA level in the thousands of copies/mL constitutes the threshold for failure. To make things more complex, it is possible that with different treatment regimens, thresholds of virologic failure that should trigger treatment switches could differ among regimens. Some guidance in this regard is provided by studies of intermittent viremia (viral “blips”) during therapy, which can be observed in up to 40% of patients receiving treatment. Studies performed with an ultrasensitive assay with limits of detection of 2 HIV-1 RNA copies/mL have shown that patients with blips reaching hundreds of copies/mL generally have higher overall plasma HIV-1 RNA levels than those without blips, although the HIV-1 RNA level remains below 50 copies/mL at all times and the blips are not associated with subsequent loss of viral suppression (Figure 1) (Havlir et al, *JAMA*, 2001). In contrast, a Swiss study has shown that patients exhibiting blips with zeniths between 1000 and 10,000 copies/mL have a higher chance of virologic failure than do patients without

blips. It is clear that achieving a nadir of HIV-1 RNA level below 50 copies/mL is important for treatment success. However, single blips in HIV-1 RNA level should not trigger therapy switches, but sustained low-level viremia in the range of 100 to 1000 copies/mL of HIV-1 RNA signals virologic failure.

It has become clear that initial viral breakthrough under treatment with some regimens is not due to viral resistance to all drugs in the regimen. This is an encouraging finding, since it suggests that not all drugs in a previously successful regimen need to be replaced, permitting a more judicious approach to treatment change and drug substitution. For example, many studies have now shown that virus resistant to lamivudine is the first to emerge in patients receiving regimens including this drug in combination with a protease inhibitor (PI) and another nRTI such as zidovudine. Thus, in many cases it may be possible to substitute another active drug for lamivudine instead of changing the entire regimen, although the validity of this approach has not yet been verified.

These and other factors suggest that approaches to early treatment failure should include careful monitoring to permit initial detection of viral breakthrough and increase chances for a successful change in treatment. The most important part of the initial response to treatment failure is to determine the reason for failure, such as emergence of resistance, inadequate adherence, toxicity, or preexistence of resistance (eg, through recent infection with drug-resistant virus). Resistance testing is of clear value in this setting to guide selection of salvage treatment. In effect, the guiding principle in this setting is to *treat early virologic failure aggressively*. Reestablishing viral suppression will optimize immune responses, limit broad cross-resistance, and preserve subsequent treatment options. With the many treatment options currently available, resuppression should be achievable in most cases. Examining examples of sequencing therapy involving popular candidates for first-line treatment, the drug mutation most likely to first emerge under an efavirenz/lamivudine/zidovudine regimen is the K103N efavirenz-associated mutation or the M184V lamivudine-associated mutation (or

both). Replacement of the affected drug only may preserve future options but risk the possibility that resistant subpopulations not detectable on drug resistance testing will emerge. On the other hand, replacement of both the nonnucleoside reverse transcriptase inhibitor (NNRTI) and lamivudine may be unnecessary if detectable resistance to only a single drug is present. Since resistance to efavirenz confers broad cross-resistance to other NNRTIs, this drug should be replaced with a PI. If resistance is due to the single M184V lamivudine mutation, activity of most other nRTIs is retained, and substitution of tenofovir or abacavir for lamivudine is a reasonable option. In the case of the lopinavir/ritonavir/lamivudine/zidovudine regimen, early resistant isolates almost invariably have only the lamivudine M184V mutation. Thus, substitution of tenofovir or abacavir is a reasonable option that also permits sparing of the NNRTI class for later use.

A recent trial comparing lopinavir/ritonavir-based and nelfinavir-based regimens provides an instructive example of both the importance of antiviral potency in limiting resistance and the rapidity with which resistant viral populations can become majority populations and result in treatment failure. In this study, the regimen of lopinavir/ritonavir/lamivudine/stavudine produced a greater rate of virologic suppres-

sion than did nelfinavir/lamivudine/stavudine. Lamivudine resistance was much higher in the nelfinavir arm than in the lopinavir/ritonavir arm (29% vs 7%) over 96 weeks of treatment (Kempf, 10th CROI, 2003). In the nelfinavir arm, lamivudine resistance was observed in significant proportions of isolates within 3 to 6 months after the last measurement of plasma HIV-1 RNA level showing suppression to below assay detection limits, highlighting the need for frequent monitoring to detect resistance in a timely manner.

### Late Treatment Failure with High CD4+ Cell Count

The guiding principle in treatment in patients with virologic failure of 2 or 3 drug classes who have an elevated CD4+ cell count and no available regimen that could achieve virologic suppression may be to *continue treatment with monitoring*. The treatment regimen may be optimized, but there should be no unnecessary increases in toxicity and adding single new drug classes should be avoided. It is important to note that recent data suggest that there is no benefit of a 4-month structured treatment interruption (STI) in this population of patients.

This approach of continuing treatment while monitoring is based in part on data showing that immunologic col-

lapse is not necessarily accompanied by persistent viremia at certain levels. One analysis has shown that maintaining partial suppression of plasma HIV-1 RNA level to between 10,000 and 20,000 copies/mL is associated with stable increases in CD4+ cell count through 4 years of such incomplete virologic suppression (Deeks et al, *AIDS*, 2002). The downside to such an approach is that incomplete viral suppression is associated with increasing viral resistance to the drugs used. Thus, continued treatment with a regimen that provides incomplete viral suppression is reasonable if CD4+ cell count declines are not observed, with benefits including the prevention of a greater, "wild-type" viral rebound and maintenance of a viral population that has less replicative fitness and, perhaps, less virulence. The primary risk associated with continuing such treatment is the evolution of resistant virus that may result in loss of future treatment options.

The recently reported findings on STI from the Community Programs for Clinical Research on AIDS (CPCRA) study 064 have dampened enthusiasm for this strategy in treatment-experienced patients. Prior studies have suggested that STI is associated with reversion of virus to wild-type and thus return of susceptibility to previously used drug classes. In the CPCRA study,

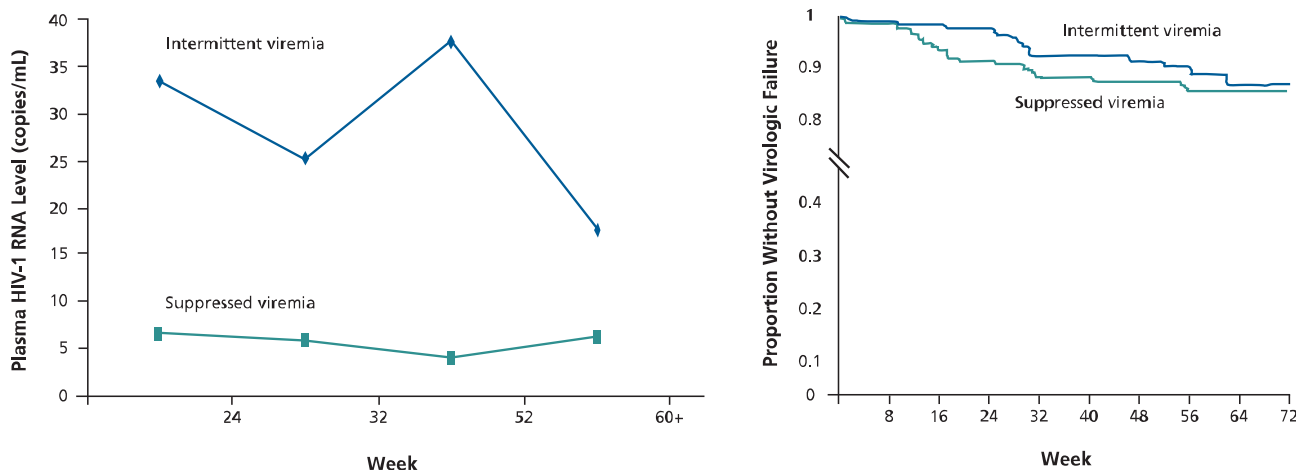


Figure 1. Plasma HIV-1 RNA level in patients with and without intermittent viremia (left) and proportions of patients remaining free of virologic failure (right). Adapted with permission from Havlir et al, *JAMA*, 2001.

270 patients with multidrug-resistant virus were randomized to a 4-month STI or no interruption and treatment with an optimized salvage regimen selected on the basis of phenotypic and genotypic evaluation (Lawrence, 10th CROI, 2003). Patients had a mean CD4+ count of 180 cells/ $\mu$ L and mean plasma HIV-1 RNA level of 5.0  $\log_{10}$  copies/mL, and 48% had triple-class drug resistance. Salvage regimens consisted of a mean of 3.6 to 3.8 drugs, including 2.7 to 2.8 active drugs, with an “active drug” defined as one to which virus was susceptible or had intermediate susceptibility on the basis of either phenotypic or genotypic assays. There was no difference between groups with regard to change in plasma HIV-1 RNA level, with changes of +0.31  $\log_{10}$  in the STI group and -0.75  $\log_{10}$  in the no-STI group at 4 months and -0.76 and -0.66  $\log_{10}$ , respectively, at 12 months. Mean changes in CD4+ cell count were better in the no-STI group, with changes of -53 cells/ $\mu$ L in the STI group versus +37 cells/ $\mu$ L in the no-STI group at 4 months and +7 cells/ $\mu$ L versus +42 cells/ $\mu$ L, respectively, at 12 months. Most disconcerting was the observation of 22 clinical endpoints (opportunistic disease or death) in the STI group versus 12 in the no-STI group (hazard ratio, 2.6;  $P=.01$ ) over mean follow-up of 11.6 months. Although most of these events consisted of candidal esophagitis, there were also cases of *Pneumocystis carinii* pneumonia (also now known as *Pneumocystis jiroveci* pneumonia) and cryptosporidiosis; 8 patients in each group died. These results suggest that STI poses significant risk of clinical disease progression in patients at this stage of HIV infection.

Although enthusiasm for STI has thus been dampened, there are encouraging data on the possibility of a strategy of partial treatment interruption, in which 1 or 2 drugs in a multidrug regimen are discontinued and partial viral suppression is maintained. The rationale for this strategy is that control of wild-type virus can be maintained with the remaining drugs in the regimen, thereby preserving immune function and reducing cumulative resistance. As reported by Deeks at the 10th CROI, although 3 of 15 patients discontinuing PI treatment but remaining on nRTI

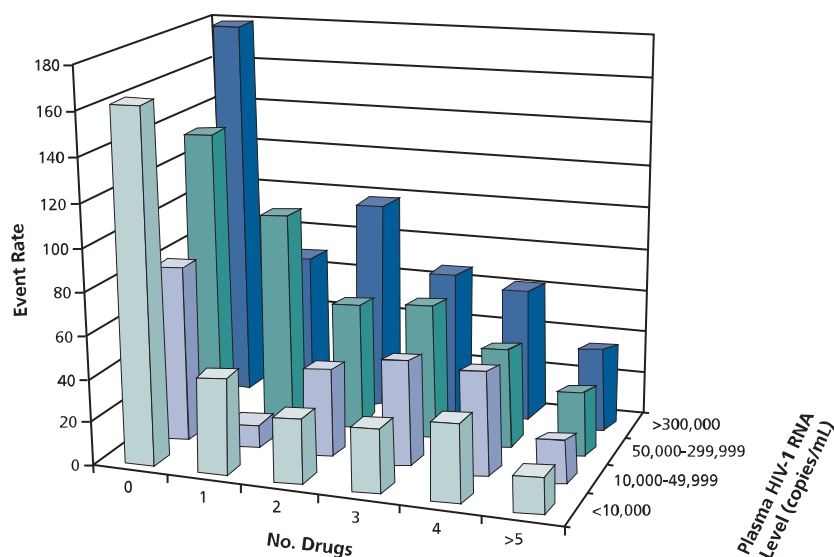


Figure 2. Clinical event rate according to number of drugs used and plasma HIV-1 RNA level (copies/mL) in EuroSIDA study. Adapted with permission from Miller et al, *J Infect Dis*, 2002.

treatment exhibited a consistent increase in viremia of greater than 0.5  $\log_{10}$  copies/mL over 24 weeks, the overall mean change in plasma HIV-1 RNA level following PI interruption in the 15 patients was only 0.005  $\log_{10}$  copies/mL per week. Conversely, 5 of 5 patients in whom nRTI treatment was interrupted while PI treatment was maintained exhibited an immediate and persistent increase in viremia of greater than 0.5  $\log_{10}$  copies/mL, with the mean change being an increase of 0.05  $\log_{10}$  copies/mL per week. Systematic studies are needed to determine if a partial treatment interruption strategy can be incorporated into clinical practice.

### Late Treatment Failure with Low CD4+ Cell Count

Based on currently available data, a principle of treatment in patients with late treatment failure and low CD4+ cell count is to *continue antiretroviral therapy*. It has been shown in numerous settings that continuation of some therapy is better than stopping therapy in terms of delaying clinical disease, and continued treatment can be used as a temporizing measure until new antiretroviral drugs become available. The EuroSIDA study, for example, has shown that use of 1 or more antiretroviral drugs protects against clinical progression to AIDS or death, even in

patients with CD4+ counts less than 50 cells/ $\mu$ L and very high plasma HIV-1 RNA levels (Figure 2) (Miller, *J Infect Dis*, 2002). There is hope in this approach, since data from initial studies on new antiretroviral classes have been encouraging.

The use of STI in this setting remains controversial. A study by Katlama et al presented at the 10th CROI indicates a pronounced benefit of STI and use of a multidrug regimen consisting of 3 or 4 nRTIs, an NNRTI, and 2 PIs plus ritonavir. Hydroxyurea was included in 71% of the patients. In this trial, 68 patients with median plasma HIV-1 RNA level of 5.3  $\log_{10}$  copies/mL and median CD4+ count of 27 cells/ $\mu$ L underwent either an 8-week STI or no STI and received the multidrug regimen. Median reductions in plasma HIV-1 RNA level were 0.29  $\log_{10}$  copies/mL in the no-STI group versus 1.1  $\log_{10}$  copies/mL in the STI group at 24 weeks ( $P=.01$ ) and 0.37  $\log_{10}$  copies/mL versus 0.80  $\log_{10}$  copies/mL, respectively, at 48 weeks. CD4+ cell count increases were markedly better in the STI group than in the no-STI group, increasing by 51 versus 7 cells/ $\mu$ L, respectively, at 24 weeks and by 69 versus 7 cells/ $\mu$ L, respectively, at 48 weeks. Predictors of virologic success in the study were reversion to wild-type virus after STI (relative hazard, 12.4), optimization of drug blood concentrations (relative hazard, 5.6), and use of

lopinavir/ritonavir (relative hazard, 6.0). There were clinical events in 10 patients in the STI group and in 6 patients in the no-STI group. It is unclear why STI appeared beneficial in this study but not in the CPCRA study in less-advanced patients. Differences between the 2 studies include the lower CD4+ cell count in the Katlama et al study; potential differences in the number of active drugs used; use of hydroxyurea differentially among treatment arms in the Katlama et al study; and the difference in STI duration (8 weeks in the Katlama study vs 16 weeks in the CPCRA study). It also appeared that in the GIGHAART study, more patients in the STI arm stayed on 6 or more drugs (47%) compared with the no-STI arm (22%). Further data on STI in this setting are needed before it can be adopted as a routine treatment strategy.

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## Suggested Reading

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