

## Perspectives

# Initiation of Antiretroviral Therapy: Current Controversies in When and with What to Start

*Initiation of antiretroviral therapy was discussed at the Los Angeles and Chicago courses in February and April by Michael S. Saag, MD, and Robert T. Schooley, MD, with the purpose of presenting the relative merits and risks of earlier initiation and deferred initiation as well as the different types of regimens appropriate for initial therapy. Dr Saag presented the rationale for deferring initiation and Dr Schooley presented the rationale for early initiation.*

## Initial Therapy: Treat Later, Keep Options Open

**Michael S. Saag, MD**

### Rationale for Later Initiation

The goals of antiretroviral therapy can be seen as 2-fold: to prevent clinical progression and to prevent or delay development of resistance. The current dilemma in the initiation of treatment stems from considerations pertaining to these goals. Dr Saag noted that to prevent the emergence of viral resistance, relatively complete viral suppression is required. However, less than maximal suppression of viral load throughout therapy can still confer a beneficial effect. A sustained reduction of 0.5 log HIV RNA copies/mL below baseline is associated with relative maintenance of CD4+ cell count over 3 years (Deeks et al, 7th CROI, 2000).

The “treat early, treat hard” approach to therapy was initially linked with the idea that complete and maintained viral suppression could result in the eradication of HIV from the body over a relatively short (eg, 3-year) treatment course. With this approach, the first treatment is envisioned as the opportunity to take the “best shot” at achieving profound suppression of viral replication, and hopefully, eradication. Based on current knowledge of HIV patho-

genesis, early and profound suppression could be expected to prevent development of resistance by limiting replication, preserving immune system integrity, and creating a higher virologic hurdle for emergence of viral resistance.

Although many aspects of this rationale remain sound, the approach also rests on assumptions concerning adherence, toxicity, pharmacokinetics, immune reconstitution, and antiretroviral effect that have proven either difficult to realize or unsupported.

- Complete adherence to complex antiretroviral regimens is difficult to maintain.

- Although serious toxicity occurs infrequently with initial treatment in early disease, prolonged treatment is associated with a number of disturbing complications.

- Drug pharmacokinetics and pharmacodynamics are subject to variability that can reduce effectiveness of treatment.

- It was believed that effective treatment initiated later in the course of disease would not be accompanied by any meaningful immune reconstitution. However, treatment initiated at relatively low CD4+ cell counts (eg, 350/ $\mu$ L) can be accompanied by immune restoration that does not seem to be clinically distinguishable from immune function at a relatively higher cell count (eg, 600/ $\mu$ L).

- Achieving HIV RNA levels below assay detection is associated with residual viral replication. Studies correlating the number of viral RNA-positive lymph node cells with plasma viral RNA level show that

plasma RNA levels of 50 copies/mL may be associated with the presence of approximately 250,000 cells that are actively producing virus. Ongoing replication in these cells is reflected by evolution in the sequence of HIV envelope in virus from patients with suppression to below 50 copies/mL for up to 24 months. Other studies have shown that the half-life of latently infected cells, which were initially thought to survive for 14 to 21 days under potent antiretroviral drug pressure, is at least 6 months and perhaps as long as 44 months, with the latter estimate indicating that complete suppression for approxi-

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The “treat early, treat hard” approach was initially linked with the idea that eradication could be achieved in a relatively short time

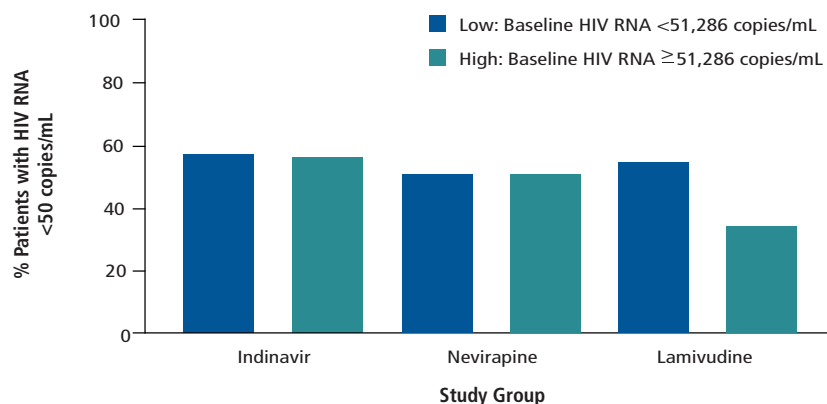
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mately 60 years would be required for viral eradication. This long period and apparent half-life likely reflects the ongoing generation of latently infected cells.

There are additional considerations that argue against universal application of very early treatment aimed at maximal suppression, including the failure of potent antiretroviral therapy to achieve HIV RNA levels below the limits of detection in a substantial proportion of patients, and the limitations of subsequent treatment options in patients in whom treatment is failing. In addition to the data regarding the relative stability of CD4+ counts in patients with maintained, relatively small reductions (0.5 to 1.01 log) in viral load, data on progression of HIV disease in untreated individuals from the Multicenter AIDS Cohort Study (MACS)

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**Dr Saag is Professor of Medicine and Director of the AIDS Outpatient Clinic at The University of Alabama at Birmingham. Dr Schooley is Tim Gill Professor of Medicine and Head of the Division of Infectious Diseases at the University of Colorado Health Sciences Center in Denver.**



**Figure 1.** Proportion of patients receiving dual nRTIs plus indinavir, nevirapine, or lamivudine with viral load below limits of detection (50 copies/mL) by baseline viral load at 48 weeks in an intent-to-treat analysis of the Atlantic study. Courtesy of Robert L. Murphy, MD.

indicate that the rate of natural progression is quite low among individuals with, for example, CD4+ cell counts of 500/μL to 750/μL and viral loads of 3000 to 10,000 copies/mL. With effective treatment, delay of progression could be expected to be markedly increased in such individuals.

Based on such considerations, a more conservative approach to treatment has become increasingly attractive. Treatment may be initiated relatively early rather than very early (eg, at CD4+ cell counts of 350/μL to 500/μL) using potent combinations intended to reduce viral load below 50 copies/mL. The selection of the specific regimen should be based on the likelihood of patient tolerance and adherence, with consideration of short-term and long-term toxicities. Initial treatment should also be selected with the aim of keeping options for subsequent treatment open, and eventual failure of the regimen should be anticipated. Most importantly, patients should understand and accept the rationale for treatment and be “ready to start” therapy.

Strategies for keeping subsequent treatment options available require consideration of which drugs could be used after the initial combination, based on what is known about class cross-resistance. Virologic failure on a particular regimen may not be associated with development of resistance to all of the drugs in the regimen—eg, as has been found for protease inhibitor and dual nucleoside reverse transcriptase inhibitor (nRTI) regimens containing lamivudine, in which lamivudine may be the only drug associated with resistance in the regimen. Regimens including a protease inhibitor, a nonnucleoside reverse transcriptase

inhibitor (NNRTI), and an nRTI are probably best avoided as initial treatment, since their use may result in few subsequent options. Regimens for initial treatment may be selected based on patient risk; for example, for patients with a relatively low viral load, triple nRTI therapy or dual nRTI/NNRTI treatment may be used. For patients with advanced disease, a 4-drug combination including 2 protease inhibitors, one of which (eg, ritonavir) is a pharmacokinetic enhancer of the other, may be optimal. Potential advantages of a protease inhibitor/dual nRTI regimen include the fact that it has the longest experience for viral suppression; disadvantages include its complexity and high pill burden, potential long-term toxicity, risk of suboptimal drug levels associated with high interindividual pharmacokinetic variability, and potential compromise of future protease inhibitor regimens. Potential advantages of a regimen combining an NNRTI and 2 nRTIs include deferral of use of a protease inhibitor and a relatively low pill burden; disadvantages include the limited long-term data on use of such regimens and the potential compromise of future use of NNRTIs.

### Protease Inhibitor-Sparing Initial Regimens

Interest in protease inhibitor-sparing regimens as initial therapy has increased with reports of longer-term complications that have been associated to some degree with this class of drugs, and with the desire to reserve the class for subsequent therapy. The Atlantic study evaluated dual nRTI regimens combined with indinavir, nevirapine,

or lamivudine (Murphy et al, 39th ICAAC, 1999). Comparable activity was observed in all 3 groups among patients with relatively low baseline viral load (<50,000 copies/mL). However, as shown in Figure 1, 48-week data from an intent-to-treat analysis indicate that the triple nRTI combination performed less well in reducing plasma viral load to levels below detection in patients with baseline viral load above 50,000 copies/mL, and the nevirapine-containing combination was comparable to that including the protease inhibitor at both lower and higher baseline viral loads. Reduced effectiveness at higher baseline viral loads is a limitation of some antiretroviral regimens. An analysis of trials using potent regimens containing indinavir, nelfinavir, nevirapine, or efavirenz showed a general trend for reduced effectiveness in lowering viral load to below 500 copies/mL in patients with higher baseline viral load.

A common question concerns the relative potency of different NNRTI-containing regimens. An analysis of studies using nevirapine-containing regimens in patients with higher viral load levels showed data similar to that in the previously mentioned study. However, the relative potencies of efavirenz- and nevirapine-containing initial regimens will be clarified in directly comparative trials, which are ongoing.

Analysis of available comparative and noncomparative data on initial potent regimens suggests comparable effects among protease inhibitor-including and protease inhibitor-sparing regimens. In a study by Staszewski and colleagues (NEJM, 1999), efavirenz/lamivudine/zidovudine was at least equal to indinavir/lamivudine/zidovudine in virologic and immunologic effects at 48 weeks; similar comparability of outcomes was reported in a trial by Katlama and colleagues assessing nevirapine/didanosine/stavudine versus indinavir/didanosine/stavudine.

A recently reported meta-analysis included intent-to-treat results of trials of triple-drug antiretroviral therapy (defined as dual nRTI plus protease inhibitor, NNRTI, or nRTI regimens) in groups of 30 or more patients with 2 or more weeks of prior drug exposure who were treated for at least 24 weeks (Bartlett et al, 7th CROI, 2000). Analysis of 48-week results indicate comparable effectiveness among the regimens in reducing viral load to levels below 400 copies/mL or to below 50 copies/mL and comparable degrees of increase in CD4+ cell count. These findings suggest

that protease inhibitor-sparing regimens (ie, an NNRTI and 2 NRTIs) may be used in initial treatment without apparent reduction in potency. Multivariate linear regression analysis indicated that among variables including drug class, baseline CD4+ cell count, and baseline viral load, only pill count was significantly predictive of reduction of viral load to 400 copies/mL or less or 50 copies/mL or less and increases in CD4+ cell count.

## Conclusions

Potent antiretroviral therapy has had a profound impact on HIV disease mortality. However, eradication is still not achievable with current regimens, the incidence of virologic failure on potent therapy increases with duration of use of the regimen, and long-term toxicities are proving to be common. The consequences of failure of potent

therapy on mortality are uncertain, but ominous. It thus appears that a reasonable approach to treatment, given the considerations discussed above, is to remember that antiretroviral therapy is an undertaking comparable to a marathon rather than a sprint, and that patients may best be served by later treatment initiation and the preservation of subsequent treatment options.

## Initial Therapy: Risks and Benefits of Earlier Initiation of Antiretroviral Therapy

**Robert T. Schooley, MD**

The rationale for early initiation of antiretroviral treatment is based on several issues as described below.

### Immunologic Damage Is Progressive and Only Partially Reversible

HIV disease progression is driven by the massive production of virions primarily in activated CD4+ cells, with CD4+ cell depletion outstripping the ability of the immune system to replenish lost cells. Although cohort data on natural history progression to AIDS according to viral load and CD4+ cell count provide an idea of risk of progression over defined periods of time in the infected population, individual risk of progression can vary according to a number of host and viral factors. Further, it remains impossible to determine in common clinical practice if a patient has undergone immunologic dam-

age that results in gaps in his or her immune repertoire that will not be restored when viral replication is suppressed. Data from ACTG 375 indicate that although patients exhibited average CD4+ cell increases of approximately 150/ $\mu$ L, the breadth of immune response indicated by CD4+ cell diversity is restricted compared with that in individuals without HIV infection. The occurrence of opportunistic conditions at relatively elevated CD4+ cell counts in some patients under antiretroviral therapy suggests that some patients do have holes in the CD4+ cell repertoire that persist despite therapy-related increases in CD4+ cell count.

### Earlier Intervention Is Associated with Greater Likelihood of Virologic Success

Perhaps the most compelling reason for early initiation of therapy is that likelihood

of virologic response predictive of durable response decreases with decreasing CD4+ cell counts and increasing baseline plasma HIV RNA levels. Data from the Swiss HIV Cohort Study, for example, indicate that each 1-log increase in plasma viral load at baseline was associated with a 25% reduction in likelihood of achieving viral load of less than 400 copies/mL (relative hazard, 0.75;  $P < 0.0001$ ) and that each 100/ $\mu$ L increase in CD4+ cell count was associated with a relative hazard of 1.04 ( $P < 0.0001$ ) for achieving this degree of viral suppression.

A similar conclusion emerges from analysis of data from a series of studies assessing the use of indinavir/zidovudine/lamivudine in different patient populations: patients with CD4+ cell counts of 50/ $\mu$ L or below, any viral load, and 6 or more months of prior zidovudine but no prior lamivudine or protease inhibitor treatment (Merck Study 039); patients with CD4+ cell counts of 50/ $\mu$ L to 400/ $\mu$ L, viral load of 20,000 or more copies/mL, and 6 or more months of prior zidovudine but no lamivudine or protease inhibitor experience (Merck Study 035); and treatment-naïve patients with CD4+ cell counts of 500/ $\mu$ L and above and viral load of 1000 copies/mL or more (Merck Study 060).

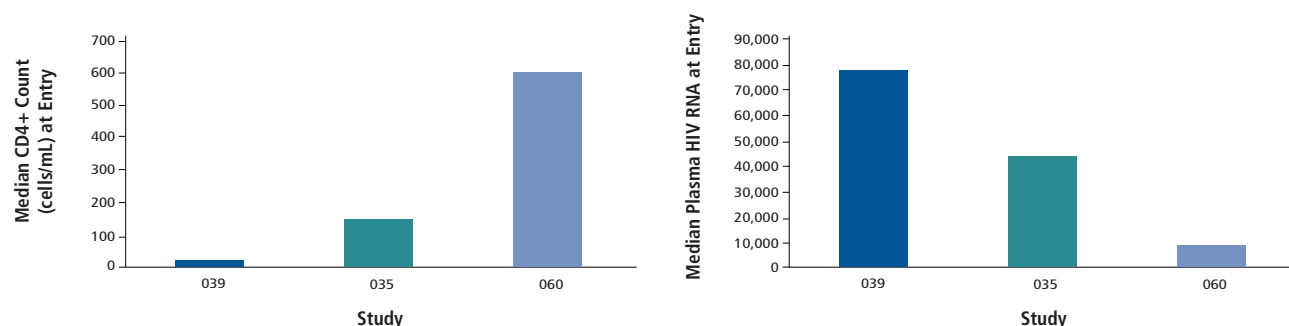


Figure 2. Median CD4+ cell counts (left) and plasma HIV RNA levels (right) in Merck studies 039, 035, and 060. Courtesy of Michael N. Robertson, MD, and Anne R. Meibohm, PhD, Merck & Co, Inc, West Point, Pa.

Median viral load levels in patients in these 3 studies were highest in the Study 039 patients and lowest in the Study 060 patients (Figure 2). The proportion of patients achieving viral load of less than 50 copies/mL on therapy was greatest in Study 060 (ie, those with the highest initial CD4+ cell counts and lowest initial viral loads), intermediate in study 035, and lowest in study 039, with the proportions remaining fairly constant over time (Figure 3). The fact that patients in the 035 and 039 studies had prior zidovudine experience should be taken into account in interpreting these findings; however, the results of the analysis suggest that treatment at higher CD4+ cell count and lower viral load is more frequently associated with initial and durable virologic response.

Suppression of viral load to as low a level as possible is important in preserving response to antiretroviral drugs (Meibohm et al, 7th CROI, 2000). Rates of decay of virus in latent reservoirs may depend on the patient population studied; patients exhibiting no or slower decline may be those in whom reseeding of the reservoir occurs as a result of lack of adherence to the antiretroviral regimen. In addition, although the relatively slow viral genetic evolution that has been described in patients with viral load below limits of detection has not yet been associated with loss of virologic control, it seems likely that such evolution will eventually result in emergence of resistant virus. The emergence of resistant virus would appear to be likely to occur more rapidly if ongoing replication at higher viral load levels is permitted.

### New Therapeutics Are in Development

There is appropriate concern regarding limitation of subsequent treatment options in patients failing initial regimens with currently available drugs. However, new agents are in development to supplement the large number of available drugs. These include drugs with reduced within-class cross-resistance, such as the protease inhibitor combination lopinavir (ABT-378/ritonavir), the nucleotide reverse transcriptase inhibitor tenofovir, and the nRTI DAPD, as well as drugs that target other than reverse transcriptase and protease, including pentafuside (T-20) and other fusion inhibitors, chemokine inhibitors, and integrase inhibitors. (See page 4 for a review of selected new investigational drugs.)

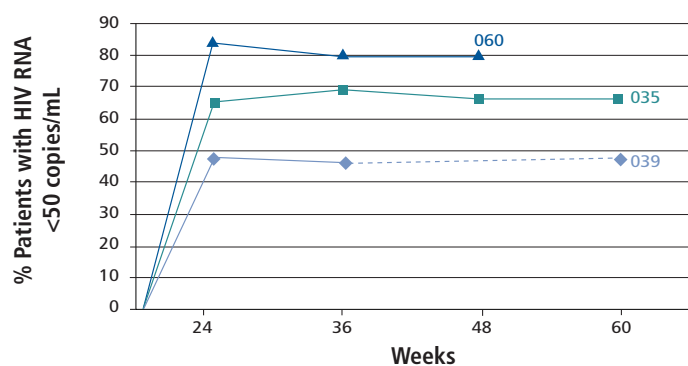


Figure 3. Proportions of patients with plasma HIV RNA levels less than 50 copies/mL during treatment over time in Merck studies 039, 035, and 060. Courtesy of Michael N. Robertson, MD, and Anne R. Meibohm, PhD, Merck & Co, Inc, West Point, Pa.

### Individualization of Drug Selection Based on Viral Genotype and Phenotype Preserves Options

Data from a number of studies have indicated that virologic failure on potent regimens is characterized by sequential drug failure, with regimen failure not implying failure of all drugs in the regimen. For example, in a study of indinavir/zidovudine/lamivudine and indinavir/efavirenz, virologic failure with the first regimen was predominantly characterized by development of the M184V lamivudine resistance mutation, with indinavir resistance mutations being relatively infrequent. Similarly, failure on the indinavir/efavirenz regimen was predominantly associated with the K103N efavirenz resistance mutation.

These and other findings indicate that regimen failure is more likely to be associated with resistance to potent drugs with a lower genetic barrier to resistance (eg, a single mutation permitting high-level resistance) and suggest that individual substitutions for failing drugs may be possible without loss of virologic effect. Individualized drug substitution and regimen intensification are currently being assessed in clinical studies. The increasing awareness that regimen failure is associated with sequential and progressive failure of the components is resulting in an evolution from the paradigm of replacing all drugs in a failing regimen to a paradigm of individualized drug selection based on monitoring for failure of individual components. This approach will permit greater preservation of treatment options, even with currently available antiretroviral drugs.

### Magnitude of Toxicities May Be Overestimated and Better Management Approaches Are Likely to Be Developed

Continued study of the long-term toxicities associated with antiretroviral therapy is required to accurately determine the incidence of and mechanisms underlying these effects. The true incidence of protease inhibitor-associated metabolic abnormalities, for example, remains to be defined, with estimates varying among different populations studied using different case definitions over various time periods. The magnitude of cardiovascular risk posed by the lipid abnormalities observed in protease inhibitor recipients is also undefined. Estimates derived from risk in the general population and degree of risk conferred by average low-density lipoprotein and very low-density lipoprotein increases in protease inhibitor recipients indicate that the 10-year risk for a cardiovascular event among 35-year-old non-smoking, normotensive men is increased from 6.18 cases/100 to 7.59 cases/100 population when the protease inhibitor-associated abnormalities are included. The 10-year risk in 35-year-old male smokers with mild hypertension is increased from 14.5 cases per 100 to 17.1 cases per 100 population when protease inhibitor-associated risk is added. Although the protease inhibitor-associated risk for cardiovascular disease may be important, it needs to be considered in the context of risk associated with withholding of antiretroviral therapy as well as the relative magnitude of cardiovascular risk conferred by traditional cardiovascular risk factors (Grunfeld, 6th CROI, 1999).



Table 1. International AIDS Society—USA Recommendations for Initiation of Antiretroviral Therapy

CD4+ Count (cells/ $\mu$ L)	Plasma HIV RNA Level (copies/mL)		
	<5000	5000-30,000	>30,000
<350	Recommend therapy	Recommend therapy	Recommend therapy
350-500	Consider therapy	Recommend therapy	Recommend therapy
>500	Defer therapy	Consider therapy	Recommend therapy

Adapted from Carpenter et al. *JAMA*. 2000.

It is likely that approaches will be developed to minimize such toxicities as their mechanisms are better understood, including more enlightened drug selection, development of new drugs with less toxic effects, and management addressing the mechanisms underlying the individual effects. Investigation of cofactors in the development of long-term toxicities is under way. In a recently reported animal study, for example, it was found that mice genetically prone to obesity exhibited metabolic abnormalities more frequently than did obesity-resistant mice with exposure to protease inhibitors. Such abnormalities in obesity-resistant mice were increased when the animals were fed a high-fat, high-calorie diet (Lenhard et al, 7th CROI, 2000). Ongoing protocols are examining measures for reversing these metabolic complications.

## Conclusions

As shown in Table 1, current recommendations for initiating antiretroviral therapy advocate deferral of therapy for patients with CD4+ cell counts above 500/ $\mu$ L and plasma HIV RNA levels less than 5000 copies/mL. Consideration of therapy is recommended in those with CD4+ cell counts above 500/ $\mu$ L and viral load levels of 5000 to 30,000 copies/mL or those with CD4+ cell counts of 350/ $\mu$ L to 500/ $\mu$ L and viral load levels of more than 5000 copies/mL. Stronger recommendations for initiation are made for all other groups stratified by CD4+ cell count and viral load. Currently, no single answer to the question of when antiretroviral therapy

should be started is appropriate for every patient. Factors that need to be considered include CD4+ cell count and viral load, toxicities, and the patient's commitment to treatment. The weight given to these factors in making decisions about initiation is likely to be influenced by advances in the understanding of risks for adverse effects with individual drugs that will alter the risk-to-benefit analysis for individual patients, and by the development of better antiretroviral agents.

## Suggested Reading

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