Perspective

Initial Antiretroviral Therapy: When and With What to Begin

At the International AIDS Society–USA course in Denver in May 2002, Donna E. Sweet, MD, discussed issues related to the ongoing question of when to initiate antiretroviral therapy in HIV-infected individuals and factors in selecting an initial drug regimen. Current treatment guidelines offer some consensus on the question of timing. Selection of the initial therapy focuses on the choice between regimens based on nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, or protease inhibitors.

The optimal time to initiate antiretroviral therapy in asymptomatic HIV-infected patients with CD4+ cell counts above 200/µL is not known. The rationale for starting therapy early includes the potential for improved virologic suppression, preservation of immune function, and reduction in sexual and perinatal HIV transmission. The rationale for later initiation of therapy includes the potential avoidance of drug resistance and adverse effects and difficulty in adherence to complex drug regimens, as well as reduced cumulative cost of treatment. Commonly considered risks and benefits associated with the approaches of early versus later initiation are shown in Table 1.

Guidelines for Initiating Treatment

Current guidelines for antiretroviral therapy reflect a movement away from early initiation of treatment (ie, at high CD4+ cell counts and detectable viral load), largely based on recognition that because of latent infection, viral eradication is not likely; that risk of near-term disease progression is low, even in relatively advanced infection; and that restoration of immunologic function can occur at lower CD4+ cell counts than previously believed. In combination with considerations regarding difficulty of adherence to antiretroviral therapy, cumulative toxicities of potent regimens, and avoidance of drug resistance to preserve future treatment options, these factors argue strongly for some delay in initiation of treatment.

Current US Department of Health and Human Services (DHHS) guidelines and International AIDS Society–USA (IAS–USA) recommendations, for example, suggest that treatment be initiated in any patient with symptomatic disease and in those with asymptomatic disease if CD4+ cell count is less than 200/µL, irrespective of plasma HIV-1 RNA level. For asymptomatic patients with CD4+ cell counts above 200/µL, the recently published IAS–USA report (Yeni et al, JAMA, 2002) recommends that the decision to begin therapy be individualized based on CD4+ count and rate of decline, plasma HIV-1 RNA level, patient interest in and potential to adhere to therapy, and risk of toxicity and drug interactions. Initiation of therapy should be considered in patients with a high plasma HIV-1 RNA level (eg, >50,000 copies/mL) or a rapidly declining CD4+ cell count. Similarly, the DHHS guidelines (available at www.hivatis.org) state that for asymptomatic patients with CD4+ cell counts of 200 to 350/µL and any plasma HIV-1 RNA level, treatment should be offered, with the proviso that controversy exists over the pros and cons of treatment in this population. For asymptomatic patients with CD4+ cell counts greater than 350/µL and plasma HIV-1 RNA above a threshold level (30,000 copies/mL on branched-DNA assay and 55,000 copies/mL on reverse transcriptase polymerase chain reaction assay), the DHHS guidelines indicate that clinical experts differ in their recommendations but many would offer treatment, whereas for those with plasma HIV-1 RNA levels below this threshold, many experts would defer treatment and

Table **1.** Risks and Benefits of Early Versus Delayed Initiation of Antiretroviral Therapy

Benefits	Risks
Early Therapy	
• Control of viral replication may be easier to achieve and maintain	• Drug-related reduction in quality of life
• Possible delay or prevention of immune system compromise	• Greater cumulative drug-related adverse events
• Lower risk of resistance with optimal viral suppression	• Earlier emergence of drug resistance if viral suppression is suboptimal
• Possible decreased risk of HIV transmission	• Limitation of future antiretroviral treatment options
Delayed Therapy	
• Avoid negative effects on quality of life	• Possible risk of irreversible immune system depletion
• Avoid drug-related adverse events	• Possible greater difficulty in suppressing viral replication
• Delay emergence of drug resistance	• Possible increased risk of HIV transmission
• Preserve maximum number of future drug options when HIV disease risk is highest	

Adapted from US Department of Health and Human Services, 2002.

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observe the patient course. This change in thinking to a more delayed approach to initiation of therapy has occurred as the problems of adherence to complex regimens (Mannerheimer et al, 13th Int AIDS Conf, 2000), potential long-term consequences of metabolic complications (Schambelan et al, *J Acquir Immune Defic Syndr*, in press), adverse impact of antiretroviral therapy on quality of life (Gill et al, *J Acquir Immune Defic Syndr*, 2002), and emergence of HIV resistance to antiretrovirals (Richman et al, 41st ICAAC, 2001) have all become more obvious.

Such recommendations are supported by a variety of data. For example, an analysis of time to death or an AIDS-defining event among 12,040 antiretroviral-naive patients beginning a 3-drug regimen at 12 centers in Europe, Canada, and the United States showed that a CD4+ cell count of 200/µL or greater at the time of starting treatment was associated with a higher probability of survival and that an HIV-1 RNA level of 5 $\log_{10}$ copies/mL or above was associated with a lower probability of survival (Egger et al, 41st ICAAC, 2001). In a retrospective review of data from 1162 patients at the Johns Hopkins University, Sterling and colleagues found that viral load at initiation of potent antiretroviral therapy was not predictive of progression to a new opportunistic infection or death (8th CROI, 2001). A CD4+ cell count of less than 200/µL was associated with a highly significant hazard ratio of 4.3 for progression compared with an initial cell count of 351 to 500/µL (referent range). A CD4+ cell count of 201 to 350/µL at initiation of therapy was associated with a statistically nonsignificant hazard ratio of 1.6 compared with the referent range.

Other studies have also shown poorer virologic response when treatment is initiated at lower CD4+ cell counts. For example, in a study reported by Levy and colleagues (8th CROI, 2001), 1266 treatment-naive patients were randomized to efavirenz or indinavir plus lamivudine/zidovudine, or efavirenz plus indinavir. The proportion of patients with plasma HIV-1 RNA levels less than 50 copies/mL at 96 weeks was markedly lower among those with CD4+ cell counts of less than 200/µL at the start of treatment than among those with higher cell counts. The Centers for Disease Control and Prevention (CDC) Adult and Adolescent Spectrum of HIV Disease Project, a record review of 5110 patients beginning 2- or 3-drug regimens in 1994 or later, showed that the hazard ratios for death at 2 years among patients with CD4+ cell counts of less than 200/µL (but not among those with counts of 200-499/µL) at the start of treatment were significantly greater than the risk for patients with counts above 500/µL (Kaplan et al, 8th CROI, 2001).

Cohort data indicate a lack of benefit of initiating therapy at CD4+ cell counts above 350/µL. In a study by Hogg and colleagues (JAMA, 2001) of 1219 patients, those who began therapy with CD4+ cell counts below 200/µL were more likely to progress to AIDS or death than those initiating with counts of at least 200/µL. Rates of disease progression or death were uniformly low in those initiating at counts of at least 200/µL. The results suggest that antiretroviral therapy may safely be initiated at CD4+ cell counts substantially lower than 500/µL, but should begin before counts drop below 200/µL. Phillips and colleagues (JAMA, 2001) found that among 3226 patients, virologic suppression could be achieved even in those with a low CD4+ count and high plasma HIV-1 RNA level prior to starting therapy. Lower CD4+ counts and higher plasma HIV-1 RNA levels at baseline were not associated with poorer virologic outcomes.

Is There an Advantage to Starting Therapy at Higher CD4+ Cell Counts?

Clinical Outcome

Not all clinicians are comfortable with delaying initiation of treatment until lower CD4+ cell counts have been reached, and there is evidence to support beginning treatment earlier. In a retrospective analysis by Chaisson and colleagues (JAMA, 2000), virologic response was assessed in 553 patients who began a triple-drug regimen after July 1996 and received at least 6 months of therapy. The patients were stratified according to initial CD4+ cell count and viral load. Virologic response was defined as plasma HIV-1 RNA level of less than 400 copies/mL within 6 months of treatment initiation and no measurement above 1000 copies/mL after initial response. The mean follow-up time was 824 days. Compared with patients with baseline CD4+ cell counts less than 200/µL, odds ratios for initial response were 0.98 (95% confidence interval [CI], 0.61-1.57) among patients with initial cell counts of 200 to 350/µL and 1.8 (95% CI, 1.10-2.96) among those with initial cell counts greater than 350/µL; respective odds ratios for durable response were 1.4 (95% CI, 0.82-2.42) and 1.9 (95% CI, 1.14-3.08). Compared with patients with baseline plasma HIV-1 RNA levels greater than 100,000 copies/mL, odds ratios for initial response were 2.5 (95% CI, 1.59-4.04) among those with baseline levels of 25,000 copies/mL or less and 1.8 (95% CI, 1.10-2.90) among those with levels of 25,000 to 100,000 copies/mL; respective odds ratios for durable response were 2.5 (95% CI, 1.45-4.35) and 1.7 (95% CI, 0.94-3.11). It was thus concluded that baseline CD4+ cell counts greater than 350/µL and plasma HIV-1 RNA levels of 25,000 copies/mL or less were associated with better initial and more durable virologic response.

> Cohort data suggest therapy may safely be initiated at CD4+ cell counts <500/µL, but should begin before counts drop to <200/µL

In a case-control prospective substudy in the Swiss HIV Cohort, Opravil and colleagues (AIDS, 2002) assessed progression to CDC category B or C disease or death in 363 antiretroviral-naive asymptomatic patients initiating therapy at CD4+ cell counts greater than 350/µL and 363 control patients not initiating therapy. At baseline, CD4+ cell counts were 487 and 498/µL and plasma

HIV-1 RNA levels were 4.2 $\log_{10}$ and 4.1 $\log_{10}$ copies/mL, respectively. Follow-up was 2.1 years among cases and 1.3 years among controls. Among cases, 29% remained on their initial antiretroviral regimen, 29% were on no regimen after follow-up, and 45% interrupted treatment at least once. Reasons for stopping at least 1 drug were virologic failure in 3.3% of cases and intolerance in 17.9%. During follow-up, CDC category B or C disease occurred in 4.7% of cases versus 17.1% of controls, and death occurred in 1.1% versus 3.3%, respectively. These findings indicate that early initiation of treatment in asymptomatic patients significantly delays disease progression and death.

Prevention of Transmission

Available data indicate that both male-to-female and female-to-male sexual transmission of HIV is related to plasma viral load. Other data indicate that viral load in genital secretions is reduced in patients on antiretroviral therapy, and modeling studies suggest that reductions in viral load would decrease the number of new infections (Blower et al, *Science*, 2000). Whether antiretroviral therapy-induced reductions in viral load actually do decrease transmission will need to be determined in a clinical trial. Further, the benefits of this effect may be tempered by increased transmission of drug-resistant virus from patients with inadequate viral suppression on treatment.

Cost-Effectiveness

Available evidence suggests that earlier initiation of antiretroviral therapy is associated with cost-savings compared with later initiation, and that antiretroviral therapy, irrespective of when it is started, compares well with other accepted therapeutic modalities in terms of cost per life-year gained. Using data from the Johns Hopkins cohort, Kauf and colleagues (1st IAS Conf HIV Pathog Treat, 2001) found that initiation of antiretroviral therapy at CD4+ cell counts greater than 500/µL was more cost-effective than initiation at 350 to 500/µL or at less than 350/µL, with a cost-effectiveness ratio of $17,879 per life-year gained. This ratio compares favorably with those for other accepted medical interventions, such as lovastatin to prevent coronary disease, screening mamography for women aged 40 to 79 years, and coronary artery bypass surgery for men aged 50 years. The investigators concluded that early initiation of treatment has the potential to reduce overall cost of treatment while improving patient outcomes. Table 2 shows this cost-effectiveness ratio and other estimates for antiretroviral therapy by CD4+ cell count at initiation.

> The question of whether antiretroviral therapy-induced reductions in viral load decrease transmission needs to be addressed in a clinical trial

Initial Regimens

Selection of Regimen

Recommendations for initial treatment included in current antiretroviral therapy guidelines may appear complicated. In considering initial treatment options, a simplified approach may be to view the decision as a choice of either 2 nucleoside reverse transcriptase inhibitors (nRTIs) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), 2 nRTIs plus a protease inhibitor (PI), or a triple-nRTI combination. The PI-containing regimens may include PIs that are pharmacokinetically boosted with low-dose ritonavir (ie, saquinavir, indinavir, lopinavir [which is coformulated with low-dose ritonavir], or amprenavir) or an unboosted PI. The boosted PI regimens may provide enhanced drug levels and may allow easier dosing schedules. A triple-nRTI initial regimen is well-tolerated and may be particularly useful in younger patients who may be prone to suboptimal adherence.

Selection of specific drugs for the initial regimen may be difficult given the many potential combinations, and may rely in part on clinical judgment regarding which regimen is likely to be better accepted or tolerated by the individual patient. Nevertheless, there are some comparative data on virologic response and duration of response that may influence decisions in this regard. In the trial by Levy and colleagues (8th CROI, 2001) noted above, approximately 80% of patients (n=422) receiving efavirenz/zidovudine/lamivudine maintained plasma HIV-1 RNA levels of less than 50 copies/mL at 96 weeks, compared with approximately 66% on indinavir/zidovudine/lamivudine (n=415) and 60% on efavirenz/indinavir (n=429).

Ruane and colleagues (1st IAS Conf HIV Pathog Treat, 2001) conducted a randomized, double-blind trial studying

Table **2.** Cost-Effectiveness Ratios for Antiretroviral Therapy From Selected Studies According to CD4+ Cell Count at Initiation

Intervention	ICER (US dollars/ life-year gained)
Antiretroviral therapy initiated when CD4+ count ≥500 cells/µL*	13,000
Antiretroviral therapy initiated when CD4+ count ≥500 cells/µL**	17,300
Antiretroviral therapy initiated when CD4+ count >500 cells/µL†	17,879
Antiretroviral therapy initiated when CD4+ count <200 cells/µL‡	20,000

ICER indicates incremental cost-effectiveness ratio. *Freedberg et al, *N Engl J Med,* 2001. **Schackman et al, *Am J Pub Health,* 2001. †Kauf et al, 1st IAS Conf HIV Pathog Treat, 2001. ‡Moore and Bartlett, *Pharmacoeconomics,* 1996.

lopinavir/ritonavir plus stavudine/lamivudine versus nelfinavir plus stavudine/lamivudine in 653 treatment-naive patients with a mean baseline plasma HIV-1 RNA level of 4.9 $\log_{10}$ copies/mL and CD4+ cell count of 259/µL. At week 60, in an intent-to-treat analysis, 63% of patients in the lopinavir/ritonavir arm achieved plasma HIV-1 RNA levels of less than 50 copies/mL compared with 51% in the nelfinavir arm (P=.001). The mean increases in CD4+ cell count were not significantly different: 246 and 224/µL, respectively. The most common adverse effects were triglyceride and other lipid level elevations.

In a trial comparing abacavir plus fixed-dose lamivudine/zidovudine with indinavir plus fixed-dose lamivudine/zidovudine, 66% of patients in the abacavir arm achieved plasma HIV-1 RNA levels of less than 400 copies/mL versus 50% of patients in the indinavir arm (P=.002) at 48 weeks on intent-to-treat analysis (Vibhagool et al, 1st IAS Conf HIV Pathog Treat, 2001).

Recent data indicate that tenofovir, the nucleotide reverse transcriptase inhibitor (n*t*RTI) recently approved by the US Food and Drug Administration, is an effective component of initial therapy. In a randomized, double-blind, placebo-controlled study (Staszewski et al, 14th Int AIDS Conf, 2002), 600 antiretroviral-naive patients received either tenofovir/lamivudine/efavirenz once daily or stavudine/lamivudine/efavirenz twice daily. Mean baseline plasma HIV-1 RNA level was 4.9 $\log_{10}$ copies/mL and mean baseline CD4+ cell count was 279/µL. In an intent-to-treat analysis at 48 weeks, plasma HIV-1 RNA level was suppressed to less than 400 copies/mL in 87% of patients in both treatment arms. Plasma HIV-1 RNA level was less than 50 copies/mL in 82% of patients in the tenofovir arm and 81% of patients in the stavudine arm.

It remains unclear whether triple-drug regimens provide adequate antiretroviral effect in patients with advanced disease, with many studies suggesting that such combinations are less effective in patients with CD4+ cell counts below 200/µL than in those with less-advanced disease. In the AIDS Clinical Trials Group 388 study, a randomized, open-label trial (Fischl et al, 9th CROI, 2002), 517 predominantly treatment-naive patients with CD4+ cell counts less than 200/µL or plasma HIV-1 RNA levels greater than 80,000 copies/mL received indinavir plus fixed-dose lamivudine/zidovudine, indinavir/nelfinavir plus fixed-dose lamivudine/zidovudine, or indinavir/efavirenz plus fixed-dose lamivudine/zidovudine. During a median follow-up of 108 weeks, the efavirenz 4-drug regimen performed better than the 3-drug regimen, and both the 3-drug regimen and the efavirenz 4-drug regimen performed better than the nelfinavir 4-drug regimen. Serious adverse effects were similar in the 3 groups but occurred earlier with the nelfinavir regimen. In another study, the 4-drug combination of abacavir and efavirenz plus fixed-dose lamivudine/zidovudine produced plasma HIV-1 RNA levels of less than 50 copies/mL at 48 weeks in 68% of patients on intent-to-treat analysis (Parenti et al, 39th IDSA, 2001).

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Selection of nRTI Backbone

Dual nRTI backbones (or nRTI/n*t*RTI backbones) are a common feature of antiretroviral regimens. Selection of the agents to be used may depend on antiretroviral effect, tolerance, and resistance patterns. In a study reported by Domula and colleagues (9th CROI, 2002), 108 patients received initial treatment with efavirenz plus one of 3 nRTI backbones: fixed-dose lamivudine/zidovudine (n=38), stavudine/lamivudine (n=35), or stavudine/didanosine (n=35). Initial mean CD4+ cell counts were 286, 166 (significantly lower than other groups), and 235/µL, respectively. After 48 weeks, plasma HIV-1 RNA level was less than 50 copies/mL in 79% of patients overall. CD4+ cell counts increased by 180/µL in the lamivudine/zidovudine backbone group, 245/µL in the stavudine/lamivudine backbone group, and 281/µL in the didanosine/stavudine backbone group. The latter regimen has been associated with considerable toxicity. In this study, the efavirenz/stavudine/lamivudine arm had the lowest drop-out rate.

With regard to potential for resistance, stavudine can select for the classical zidovudine resistance mutations, and such mutations have been detected in zidovudine-naive patients. A study with stavudine-experienced, zidovudine-naive viremic patients showed that nRTI resistance mutations (specifically D67N and L210W) were present in 41% of 29 patients receiving stavudine/didanosine versus 33% of 106 patients receiving stavudine/lamivudine for a longer duration; multi-nRTI resistance mutations (Q151M, T69N, and 69SS insertion complex) were found in 20.6% versus 5.6%, respectively. These findings suggest that the stavudine/lamivudine combination may be less likely to select for nRTI-resistant mutants than the stavudine/didanosine combination (Ross et al, 9th CROI, 2002).

Advantages and Disadvantages of Initial Regimens

Table 3 summarizes potential advantages and disadvantages of initial treatment with triple-nRTI, NNRTI-based, and PI-based combinations. Advantages of each include sparing treatment with other drug classes for later use. Clinical endpoint data are lacking for the triple-nRTI and NNRTI-based approaches.

Dosing requirements for many of the drugs used in all of the potential regimens have improved markedly over the past several years. For example, among nRTIs, didanosine can now be given at 400 mg once daily (pill or suspension), zidovudine at 300 mg twice daily, fixed-dose lamivudine/zidovudine as one 150-mg/300-mg pill twice daily, and fixed-dose lamivudine/zidovudine/abacavir as one 150-mg/300-mg/300-mg pill twice daily. Among NNRTIs, nevirapine can be given at 400 mg once daily, with the dose of efavirenz remaining at 600 mg

once daily. Among PIs, the boosted combinations of ritonavir/saquinavir are given at 400 mg/400 mg twice daily, ritonavir/indinavir at 400 mg/400 mg or 200 mg/800 mg twice daily, and ritonavir/amprenavir at 200 mg/600 mg twice daily. Nelfinavir alone can now be given at 1250 mg twice daily.

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Table **3.** Advantages and Disadvantages of Triple-nRTI, NNRTI-Based, and PI-Based Initial Therapy

Advantages	Disadvantages
Triple-nRTI	
• Easier to use and adhere to • Avoids PI and NNRTI adverse effects* • Limited cross-resistance within the class • Drug interactions are manageable • Preserves PIs and NNRTIs for later use	• Clinical endpoints are unknown • Long-term virologic efficacy may be suboptimal with high baseline viral load
NNRTI-Based	
• Avoids PI-related adverse effects* • Generally easier to use and adhere to • Fewer drug-drug interactions • Preserves PIs for later use	• Clinical endpoints are unknown • Resistance to NNRTIs requires single or few mutations • Emergence of cross-resistance for entire NNRTI class
PI-Based	
• Documented clinical, virologic, and immunologic efficacy • Benefit despite viral breakthrough • Resistance requires multiple mutations • Targets HIV at 2 steps of viral replication • Preserves NNRTIs for later use	• May be difficult to use and adhere to • May be associated with long-term adverse effects (lipodystrophy, insulin resistance and hyperlipidemia)* • Mild to severe inhibition of cytochrome P450 system • Emergence of cross-resistance with other PIs

NNRTI indicates nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. *Some adverse effects attributed to PI-based therapy, such as metabolic abnormalities, have not been proven to be strictly associated with the use of PI-containing regimens. Metabolic abnormalities have also been described, albeit uncommonly, in patients on nRTIs alone and in patients on no antiretroviral therapy. Adapted from US Department of Health and Human Services, 2002.

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