

Perspective

Antiretroviral Therapy: Select Lessons From Recent Studies

Our understanding of HIV pathogenesis continues to evolve and form the foundation for antiretroviral treatment and drug development strategies. There is an increased focus on improving drug pharmacodynamics and tolerability and simplicity of drug regimens to optimize viral suppression and preserve immune function. In terms of antiretroviral therapy using current treatment options, the CD4+ cell count at initiation of treatment appears to be the most powerful discriminator of risk for disease progression. Newer drug regimens have better rates of virologic response to a plasma HIV-1 RNA level below 50 copies/mL on intent-to-treat analyses than prior standard regimens, which likely reflects improvements in simplicity, tolerability, and pharmacodynamics rather than improved potency per se. With regard to particular initial treatment choices, recent trials evaluating nevirapine (once or twice daily) with or without efavirenz, triple nucleoside reverse transcriptase inhibitor regimens, and didanosine EC/tenofovir, among others, have provided insights. This article summarizes a presentation given by Michael S. Saag, MD, at the May 2003 International AIDS Society–USA course in Washington, DC. The presentation focused on selected new data that provide insights in clinical management, particularly with regard to initiating antiretroviral therapy.

HIV Pathogenesis: The Background for Devising Treatment Strategies

Our understanding of HIV pathogenesis and its relationship to antiretroviral treatment has undergone continual evolution. The concepts of HIV pathogenesis affect strategies for antiretroviral therapy as well as strategies for drug development.

HIV-infected cells produce virions that predominantly target activated CD4+ T lymphocytes. After infection, an activated CD4+ T cell has a life span of approximately 1 day, during which it produces a multitude of virions, and after which it is essentially replaced by another newly infected CD4+ T cell from the activated cell pool. Antiretroviral drugs prevent new infection of activated CD4+ cells (whether by preventing formation of new virions as with nucleoside and nonnucleoside reverse transcriptase inhibitors, preventing infectivity of virus as with protease inhibitors, or blocking viral entry as with fusion inhibitors). Several years ago, it was believed that viral eradication would be possible if infection of

new cells could be blocked completely (by 100%) and this blockade could be sustained for a sufficient period of time to allow complete loss of all previously infected cells. Based on the assumption

that the half-life of latently infected CD4+ cells was 14 to 28 days, it was calculated that eradication could occur in 3 to 5 years. This provided much of the rationale for the very early and very aggressive use of antiretroviral therapy recommended at that time. It is now known that these latently infected cells live for anywhere from 6 to 40 or more months. Even with 100% prevention of new infection, complete eradication would require some 60 years of continuous treatment and thus, full eradication, or cure, currently is not a practical goal. Further, 100% blockade of new infection is an elusive goal, with a variety of data showing some degree of ongoing, yet low-level, viral replication even with profound viral suppression (Figure 1).

Several years ago, it was generally believed that the primary mechanism of

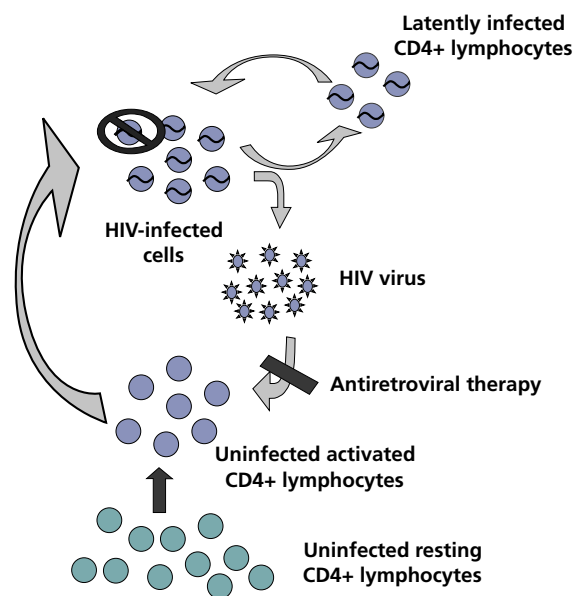


Figure 1. HIV predominantly infects activated CD4+ T lymphocytes. An activated cell dies after approximately 1 day of productive infection and is replaced by another activated cell that is highly likely to be infected (since it is activated in a milieu teeming with virions). Effective antiretroviral therapy prevents infection of the activated cell, allowing replacement of the virus-producing cell with a cell that is not infected. Viral replication can be profoundly reduced but eradication is not a practical goal, given the extended survival of latently infected resting lymphocytes and the low-level viral replication in the presence of profound viral suppression. Figure courtesy of Dr Michael Saag.

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cell death was a direct cytopathic effect of the virus. Although this mechanism likely contributes to cell death, recent evidence suggests that the predominant mechanism may be the action of CD8 + cytotoxic T cells and other effector cells in killing infected cells. With prevention of new infection under effective antiretroviral therapy, the processes resulting in cell lysis might also be downregulated. The rapid decay in viral kinetics under antiretroviral therapy, therefore, simply reflects the replacement of an infected cell that is actively producing virus with a newly infected cell. If therapy is stopped, production of virus is reestablished in activated cells no longer protected by antiretroviral therapy, with levels of viral replication usually returning to the set point observed previously.

This set point appears to be the product of the interaction of virus-producing cells and activity of cytotoxic CD8 + lymphocytes, which is governed by host genetics such as chemokine receptor genetics and HLA haplotypes. Infected activated cells therein produce multitudes of virions in an environment largely consisting of inactivated lymphocytes. At steady state, no matter how many virions an infected cell produces during its 1-day lifetime, it is effectively replaced with only a single newly infected activated cell at the time it dies. The viral set point thus represents an equilibrium between the rates of new cell infection and infected cell death. The plasma HIV RNA level directly reflects the total number of infected cells in an individual, with the level of replication remaining relatively constant as the number of newly infected cells remains constant. The HIV-1 RNA level as measured in plasma simply represents a spillover of virus from lymphatic tissue into the bloodstream and there is likely no replication occurring in the peripheral blood per se. Under conditions of antiretroviral therapy, the “replacement” lymphocyte is protected, resulting in the overall “loss” of a virus-producing cell and a proportionate decline in the number of virions produced. This decline in replication is reflected in the dramatic decrease in plasma HIV-1 RNA level, which accurately reflects the reduction in the level of replication in lymphatic tissues.

This conception of HIV pathogenesis

is relevant to management strategies in a variety of ways. It sharpens focus on the importance of ensuring that antiretroviral drugs are penetrating into the cells that need protection or, as in the case of protease inhibitors, into cells that are already actively infected. Drug pharmacodynamics are crucial to the strength of protection provided to susceptible cells by antiretroviral therapy. Efforts are ongoing to better understand the pharmacokinetics and pharmacodynamics of drugs within cells to determine if there are ways to increase intracellular residence time by overcoming cellular mechanisms that retard drug entry or accelerate extrusion of drug from the intracellular compartment. It may be that virologic failure occurs in fully adherent patients because of induction of cellular pump systems over time by the antiretroviral drugs themselves.

This conception of pathogenesis also emphasizes the emergence of viral resistance as a chance phenomenon. Under conditions of incomplete viral suppression, a genetic variant of the virus that is resistant to a single drug can, by chance, be produced and infect an activated cell. The likelihood of such an occurrence increases with increasing levels of viral replication in the face of ongoing drug pressure on the virus, such as what might occur with intermittent adherence. In fact, the least amount of risk of resistance emergence is present when the plasma HIV-1 RNA is maintained at levels below 50 copies/mL. Triple-drug antiretroviral therapy provides additional protection for the activated cell via coverage for the

chance development of a single mutation to 1 of the drugs in the regimen. Although it seems a heretical idea in the current treatment era with available drugs, effective monotherapy could be possible with optimized pharmacodynamics and thus is the subject of ongoing investigation. The pathogenesis of HIV suggests, however, that this is not likely to be a successful long-term strategy.

Initial Antiretroviral Strategies: Lessons From Recent Studies

Predicting Successful Response

Data are emerging that show that baseline CD4 + cell count may be the best predictor of response to initial antiretroviral therapy. The Multi-ART Cohort Collaboration Study observed more than 12,000 patients beginning antiretroviral therapy for long-term outcomes. Baseline CD4 + cell count was the best discriminator for predicting AIDS-free survival (Figure 2, left). By comparison, only plasma HIV-1 RNA level greater than 100,000 copies/mL provided any additional discrimination of risk (Figure 2, right). Hazard ratios for progression to AIDS or death using a multivariable Cox model for baseline predictive factors are shown in Table 1. Figure 3 shows the probability of progression to AIDS or death by year according to CD4 + cell count stratum and plasma HIV-1 RNA level stratum among patients with lower risk according to age, history of injection drug use, and Centers for Disease

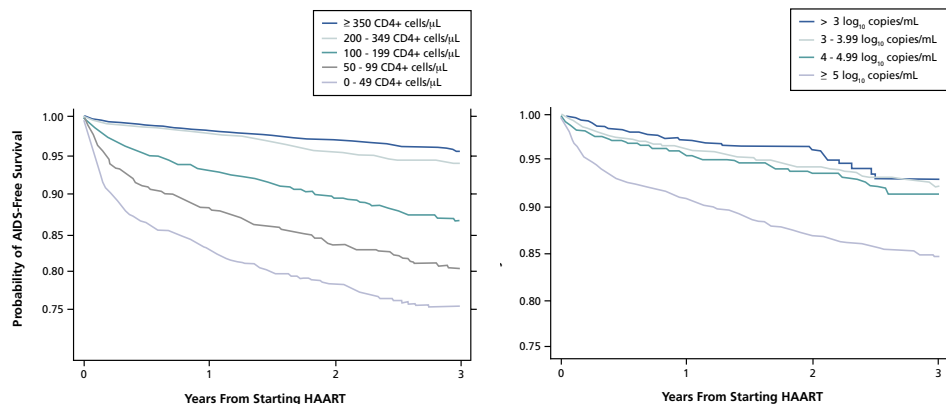


Figure 2. AIDS-free survival by baseline CD4+ cell count (left) and baseline plasma HIV-1 RNA level (right) in the Multi-ART Cohort Collaboration Study, covering a period of 3 years of patient treatment with antiretroviral therapy. Adapted from Hogg et al, JAMA, 2001.

Table 1. Significant Discriminators of Risk for Progression to AIDS or Death in the Multi-ART Cohort Collaboration Study

Discriminator	Hazard Ratio (95% CI)
Age	
≥ 50 years	1
< 50 years	0.72 (0.62 to 0.84)
Risk Behavior	
Injection drug use	1
Other	0.68 (0.59 to 0.79)
CDC Disease Stage	
C	1
A/B	0.70 (0.61 to 0.81)
CD4+ cells/μL	
0-49	1
50-99	0.75 (0.63 to 0.90)
100-199	0.53 (0.44 to 0.63)
200-349	0.25 (0.20 to 0.30)
≥ 350	0.18 (0.14 to 0.22)
Log₁₀ HIV-1 RNA copies/mL	
≥ 5	1
< 5	0.75 (0.63 to 0.90)

CDC indicates Centers for Disease Control and Prevention; CI, confidence interval. Data are from Egger et al, *Lancet*, 2002.

Control and Prevention (CDC) disease stage. The highest probabilities of progression were observed in patients with the lowest CD4+ cell counts and higher HIV-1 RNA levels (12.4%, 17.0%, and 20.3% at 1, 2, and 3 years, respectively). The lowest risk of progression was observed in patients with a CD4+ cell count of 350/μL or greater and an HIV-1 RNA level below 5 log₁₀ copies/mL (1.5%, 2.5%, and 3.4% at 1, 2, and 3 years, respectively). Such findings have implications for when to start antiretroviral therapy. The CD4+ cell count has, over the last few years, become the primary trigger for when to begin antiretroviral therapy. Delaying therapy until the CD4+ cell count declines to 200/μL clearly is too late, but the optimal CD4+ count above 200/μL remains unknown. Current guidelines suggest a CD4+ cell count threshold somewhere between

200/μL and 350/μL, however, the above findings suggest that there is benefit to initiating therapy at higher CD4+ cell counts, especially among those with very high HIV-1 RNA levels. These findings are consistent with experimental data indicating that very high HIV-1 RNA levels are associated with reduced function of immune system effector cells, suggesting that the presence of large amounts of virus has an immunosuppressive effect. In recent years, there has been a trend toward delaying initiation of therapy until relatively low CD4+ cell counts owing to the low risk of opportunistic infections at moderately low cell counts. However, based on findings such as those in the current study, it appears that the pendulum is swinging back toward earlier initiation of therapy. Indeed, continued long-term outcome evaluations may indicate that it is best to initiate therapy when CD4+ cell counts are still above 400/μL.

Factors in Selecting Initial Therapy

Numerous factors are important in choosing the initial antiretroviral regimen, including potency, simplicity, tol-

erability, “forgivability” (ie, less deleterious effect of a single missed dose), and salvageability (ie, predicted resistance profile at time of virologic failure, which affects subsequent treatment options).

The single most important factor is potency. However, assuming equal potency of regimens, then tolerability and simplicity are the next primary considerations. Given the relatively equal potency of most current regimens, tolerability emerges as the most important factor in maintaining effective treatment on a day-to-day basis: drugs do not work if people do not take them. This brings the focus to “forgivability.” It is human nature to miss doses of medications. Drugs with pharmacokinetic/pharmacodynamic properties that allow prolonged intracellular half-lives are less likely to lose antiretroviral pressure in the setting of a single missed dose and, therefore, would clearly be advantageous.

A meta-analysis performed several years ago indicated that only 46% of patients were able to achieve an HIV-1 RNA level below 50 copies/mL at 48 weeks using intent-to-treat analyses. More recent studies of newer regimens

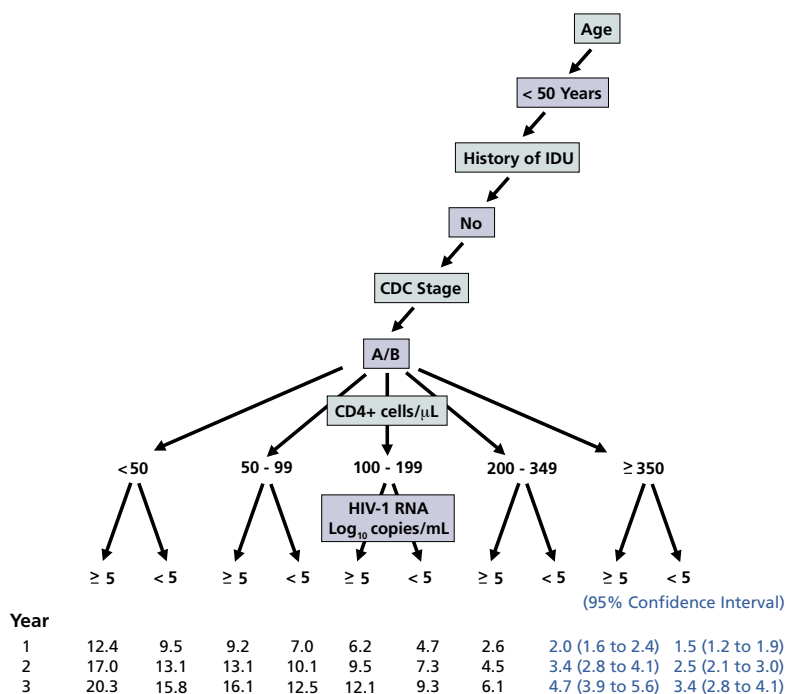


Figure 3. The probability of progression to AIDS or death by year of study in patients aged less than 50 years, with no history of injection drug use (IDU), and with Centers for Disease Control and Prevention (CDC) disease stage A/B according to baseline CD4+ cell count and HIV-1 RNA level in the Multi-ART Cohort Collaboration Study. Data are, in part, published in Egger et al, *Lancet*, 2002; figure courtesy of Dr Matthias Egger.

show dramatically better 24-week response rates than those considered in the meta-analysis (Figure 4). These newer regimens are probably not more potent than previously studied protease inhibitor-based triple-drug regimens. Rather, it is more likely that improvements in tolerability and “forgivability” have accounted for the ability to achieve these greater levels of virologic response.

Relative Effectiveness of Nevirapine- and Efavirenz-Containing Regimens

The 2NN study compared nevirapine 400 mg once daily, nevirapine 200 mg twice daily, efavirenz 600 mg once daily, and the combination of nevirapine 400 mg/efavirenz 800 mg once daily along with stavudine/lamivudine in 1216 antiretroviral-naive patients with an HIV-1 RNA level above 5000 copies/mL and any CD4+ cell count. No significant differences in proportions of patients reaching an HIV-1 RNA level below 50 copies/mL were seen between any of the regimens on intent-to-treat analysis, with proportions of patients reaching this level ranging from 63% with the dual nonnucleoside reverse transcriptase inhibitor (NNRTI) combination to 70% with the nevirapine once-daily regimen and the efavirenz

regimen. However, there were differences in rates of discontinuation or interruption due to clinical adverse events: 15.5% in the efavirenz group, 21.2% in the nevirapine twice-daily group, 24.1% in the nevirapine once-daily group, and 29.7% in the combination group ($P < .001$). There was also an overall difference in rates of laboratory grade 3 or 4 hepato-biliary toxicities among groups: 4.5% in the efavirenz group, 7.8% in the nevirapine twice-daily group, 8.6% in the combination group, and 13.2% in the nevirapine once-daily group ($P = .002$). These findings suggest no added benefit and worse tolerance with the dual NNRTI nevirapine/efavirenz combination, at least at the doses studied, and suggest that nevirapine twice daily may be safer and better tolerated than the once-daily nevirapine regimen.

Relative Effectiveness of Abacavir-Containing Triple-Nucleoside Initial Therapy

ACTG 5095 compared efavirenz, abacavir, or the efavirenz/abacavir combination along with zidovudine/lamivudine as initial antiretroviral therapy. Virologic failure was defined as an HIV-1 RNA level above 200 copies/mL at week 16. The trial used rejection of a

non-inferiority null hypothesis with O'Brien-Fleming stopping rules. At the second Data and Safety Monitoring Board review of the study, there were no safety issues with any of the regimens. However, the trial was stopped because of demonstrated inferiority of the abacavir-containing triple-drug regimen compared with the other 2 regimens on the basis of rates of and time to virologic failure. Although this trial provides evidence that the lamivudine/zidovudine/abacavir (fixed dosage) combination is inferior as initial therapy, the response rate with the combination was still quite high (74% less than 50 copies/mL at 24 weeks), higher in fact than any response rate previously reported with the combination and much higher than the 46% response rate reported in the meta-analysis study reported above. Therefore, the combination might still be advocated for use in initial treatment in selected patient populations on the basis of simplicity of use. Further, the results of this study do not clearly support changing the regimen or enhancing it by adding efavirenz if patients are already responding to the lamivudine/zidovudine/abacavir combination with an HIV-1 RNA level below 50 copies/mL. Rather, the results from this study should be discussed with such patients and individual decisions made between the patient and the treating provider.

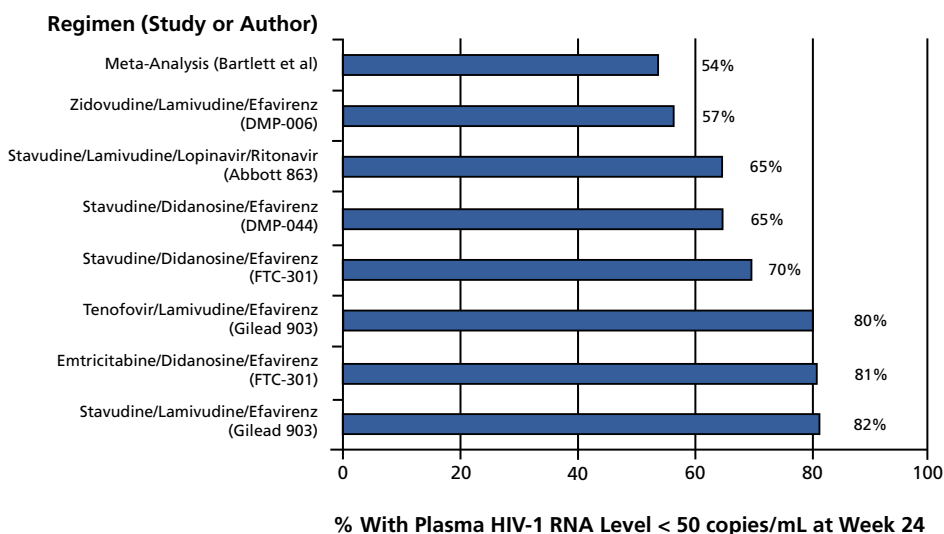


Figure 4. Proportions of patients achieving an HIV-1 RNA level below 50 copies/mL at 24 weeks on intent-to-treat analyses (non completer = failure) in recent studies compared with an earlier meta-analysis. Figure courtesy of Dr Michael Saag.

Combined Use of Didanosine EC and Tenofovir

There is confusion in the clinical setting about how didanosine EC and tenofovir should be used together. Tenofovir significantly boosts didanosine concentrations, and therefore the use of didanosine EC 400 mg with tenofovir 300 mg may markedly increase risk of pancreatitis. Pharmacokinetics studies evaluating didanosine alone at 400 mg and didanosine (at various doses)/tenofovir combinations with and without food indicate that the appropriate dose of the combination is didanosine EC 250 mg/tenofovir 300 mg once daily, for patients weighing more than 50 kg; those patients weighing less than 50 kg should have the didanosine dose reduced to 200 mg/per day. The combination can be given with food or fasting.

Combined Use of Tenofovir and Abacavir

At the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment in Paris, Charles Farthing presented results of a small pilot study evaluating the relative activity of a novel, once-daily regimen of abacavir/lamivudine/tenofovir in patients naive to antiretroviral therapy. Surprisingly, only 8 of 19 (42%) patients had a successful virologic response, defined as a greater than 2-log drop in HIV RNA by week 8, or loss of this effect (virologic rebound) after initial suppression.

Soon after this presentation, Glaxo-SmithKline released a “Dear Healthcare Provider” letter reporting data from an ongoing study, EES 30009, that demonstrated similar findings. In EES 30009, patients naive to antiretroviral therapy were randomized (1:1) to receive abacavir/lamivudine with either efavirenz or tenofovir. An unplanned interim evaluation of the data revealed a surprisingly large difference in virologic outcomes: only 5 of 92 patients (5%) in the efavirenz arm experienced virologic failure compared with 50 of 102 patients (49%) in the tenofovir arm. Taking these data together with the Farthing study results, there appears to be a negative interaction among abacavir, lamivudine, and tenofovir. However, since numerous studies comparing abacavir and lamivudine together with other agents, as well as various studies comparing lamivudine and tenofovir combined with other agents, have not demonstrated such high rates of failure, it appears that the principal negative interaction might be between abacavir and tenofovir. This interaction could take the form of interference with drug absorption or metabolism, yet the most likely interaction seems to be at the level of intracellular concentrations of active drug(s) in the triphosphate form (similar to the type of negative interaction seen between zidovudine and stavudine).

Further studies are needed to fully elucidate the mechanism(s) responsible for these relatively poor virologic outcomes. Until then, patients on combination regimens containing abacavir and tenofovir, with or without lamivudine, should be monitored very carefully and this combination should be avoided in new regimens.

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Suggested Reading

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