

## Perspective

# Initiation of Antiretroviral Therapy: Implications of Recent Findings

*A number of reports related to initiation of antiretroviral therapy have been reported recently. Available data continue to support the practice of not starting therapy for asymptomatic patients who have CD4+ cell counts above 350/μL, and consideration for initiating antiretroviral therapy below this point, but before the count drops to 200/mL. In terms of initial regimens, some data suggest better virologic response rates with nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens than with protease inhibitor-based regimens. The differences are likely due to better tolerability of NNRTI-based regimens. Small studies in treatment-naïve patients have shown poor virologic outcome in patients receiving certain regimens, such as abacavir/lamivudine/tenofovir or didanosine/lamivudine/tenofovir, yet better outcomes in patients treated with abacavir/lamivudine/zidovudine/tenofovir. These findings appear to be explained by the differing effects of the reverse transcriptase K65R mutation on different drugs. Other recent studies suggest fewer metabolic adverse effects with emtricitabine-containing treatment than with stavudine-containing treatment, comparable virologic outcomes with once-daily and twice-daily abacavir regimens; comparable virologic outcomes with once-daily and twice-daily lopinavir/ritonavir regimens, and an association between didanosine 400 mg/tenofovir regimens and declines in CD4+ cell counts despite viral suppression. This article summarizes a presentation on initiation of antiretroviral therapy by Michael S. Saag, MD, at the International AIDS Society–USA course in New York in March 2004.*

New data have become available since early 2004 that impact the strategies for initiating antiretroviral therapy in HIV-infected individuals. Information continues to support initiating therapy for asymptomatic patients somewhere between 200 and 350 CD4+ cells/μL, but when, in this range, is the optimal time to start remains undefined. Despite this uncertainty, waiting until the CD4+ count drops below 200 cells/μL is clearly too late.

With regard to the best regimen to use as initial therapy, results of several trials in antiretroviral-naïve and antiretroviral-experienced patients identify specific drugs or combinations to strongly consider and some regimens to definitely avoid. The following summarizes some of these new data and how they may impact current clinical practice.

### When to Initiate Therapy

The optimal time to initiate antiretroviral therapy in HIV-infected individuals

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remains imprecisely defined beyond the currently accepted and well-established CD4+ cell count threshold levels. Treatment should be started in all patients with symptomatic disease regardless of CD4+ count. Natural history data continue to show that disease progression is slow in patients with CD4+ cell counts greater than 350/μL, suggesting that treatment can be delayed in asymptomatic patients in this setting. The probability of AIDS-free survival according to baseline CD4+ cell count in the ART Cohort Collaboration, now involving tens of thousands of patients, is shown in Figure 1 (Eggers et al, *Lancet*, 2003).

The use of viral load as a marker of when to initiate therapy remains controversial. In the Antiretroviral Therapy (ART) Cohort Collaboration, accelerated disease progression occurred in patients with plasma HIV RNA levels greater than 5 log<sub>10</sub> (100,000) copies/mL. However, it is possible that more frequent monitoring of patients with higher CD4+ cell counts who have elevated viral load values may be preferable to starting therapy simply based on viral load values alone.

Unfortunately, the issue of when to initiate therapy is not one typically

faced with individuals presenting with HIV infection in many clinics. For example, at the University of Alabama at Birmingham 1917 Clinic, the median CD4+ cell count at first contact is approximately 100/μL; only 15% of patients present with CD4+ counts above 350 cells/μL. Among those patients presenting with higher CD4+ cell counts, the majority are pregnant women who were tested for HIV as part of their prenatal evaluations.

It is tragic that HIV infections are not being identified earlier in the disease course, because there is higher mortality among patients starting therapy with CD4+ counts below 200 cells/μL. The failure to identify patients and start their treatment earlier in their disease course in current practice argues against simple voluntary testing and argues for the provision of opt-out testing as a strategic national approach to minimize mortality and potentially to reduce the number of new infections.

### Considerations in Selecting the Initial Regimen: Recent Findings

#### Tolerability and Virologic Effectiveness

Most antiretroviral regimens used as initial treatment are relatively equipotent in terms of their virologic activity. One exception to this tenet is illustrated by the results of the AIDS Clinical Trials Group (ACTG) 5095 study, wherein a triple-nucleoside reverse transcriptase inhibitor (nRTI) regimen did not perform as well as regimens anchored with a nonnucleoside reverse transcriptase inhibitor (NNRTI) agent (Gulick, *NEJM*, 2004). In other studies, however, careful evaluation of the trial results suggests that differences in outcomes are attributable to subtle differences in tolerability among the regimens used. This is especially true in asymptomatic patients, in whom adverse effects such as nausea, cramping, headache, and

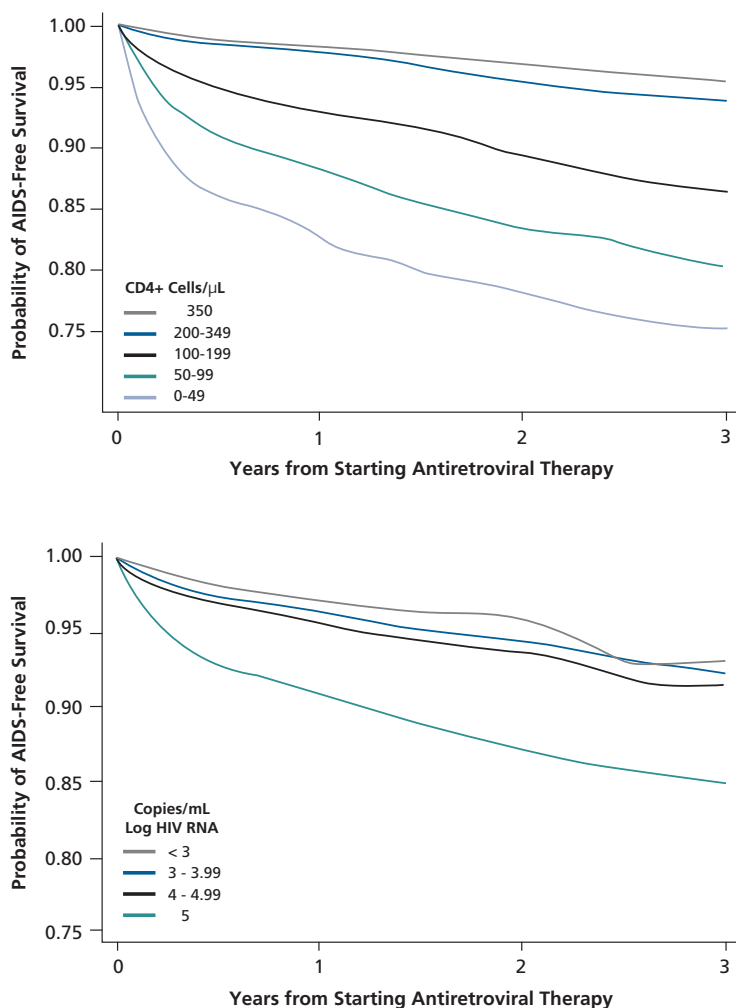


Figure 1. AIDS-free survival by CD4+ count (cells/μL) (top) and plasma log<sub>10</sub> HIV RNA (bottom) at baseline in the ART Cohort Collaboration. Adapted in part from data in Egger et al, *Lancet*, 2003.

general dysphoria can have a profound impact on their attitudes toward taking medication.

Most patients base their daily decisions about taking medication on how they feel rather than on potential long-term consequences. For those patients experiencing even subtle toxicities, the association of a missed dose of medication with feeling better due to the absence of adverse effects serves to reinforce the behavior of missing doses. Outcomes assessed by intent-to-treat analyses in clinical trials of initial regimens are influenced by a number of factors, the most critical of which is whether the patient actually took the assigned medication. Recent studies demonstrate that the highest virologic response rates (in terms of reduction of

plasma HIV RNA to less than 50 copies/mL at 24 weeks by intent-to-treat analyses) are observed with NNRTI-based regimens, particularly efavirenz-based regimens, rather than with protease inhibitor (PI)-based regimens. In several studies, efavirenz-based regimens achieved HIV RNA response rates of less than 50 copies/mL at 48 weeks (intent-to-treat analyses) reaching or exceeding 80%. In contrast, no randomized controlled study of a PI-based regimen has been reported (intent-to-treat analysis) to produce such a virologic response rate greater than 70%. It is likely that this difference in efficacy reflects overall poorer tolerability of PIs, since as-treated analyses of groups receiving PI-based treatment tend to show successful virologic responses in

more than 90% of patients. Among relatively equipotent regimens, those that are better tolerated produce better treatment outcomes. Therefore, a key consideration of initial therapy is short- and long-term tolerability.

### Tenofovir-Containing Triple-nRTI Regimens and the K65R Mutation

Although the ACTG 5095 study demonstrated inferior activity of the triple-nRTI regimen of zidovudine/lamivudine/abacavir compared with an efavirenz-based regimen, the overall activity of the triple-nRTI regimen was comparable to results of PI-containing regimens by intent-to-treat analyses. However, this does not mean that all triple-nRTI regimens have similar effectiveness. A recent study (TONUS) showed poor virologic outcome with the triple-nRTI combination of once-daily abacavir/lamivudine/tenofovir (Landman et al, 11th CROI, 2004). In this study, HIV RNA level was not reduced to below 400 copies/mL in the majority of patients by week 12, and virologic failure occurred in 12 of 36 patients at week 24. The conclusion from this study was that there might be an unanticipated interaction between abacavir and tenofovir.

In follow-up to this concept, Jemsek and colleagues (11th CROI, 2004) evaluated a once-daily regimen of didanosine/lamivudine/tenofovir in 20 treatment-naïve patients. Virologic results in this study were also surprisingly dismal: only approximately 25% had a decrease of greater than 1 log<sub>10</sub> in plasma HIV RNA after 12 weeks and approximately 20% of patients had an increase in plasma HIV RNA level. Such poor responses were not expected with triple-nRTI combinations. Genotypic analysis showed that half of the patients had the M184V lamivudine-associated resistance mutation and half had the M184V mutation plus the K65R resistance mutation. Phenotypic analysis showed reduced susceptibility to lamivudine in each of 19 patients tested, to didanosine in 6 patients (associated with the M184V and K65R mutations), and to abacavir in 6 patients (associated with the M184V and K65R mutations). There was no reduced susceptibility to zidovudine, tenofovir, or stavudine.

A subanalysis of the TONUS study (Landman et al, 11th CROI, 2004)

**Table 1.** Proportions of patients receiving abacavir/lamivudine/zidovudine/tenofovir who had HIV RNA levels below 400 copies/mL and below 50 copies/mL at 24 weeks in study COL40263 (intent-to-treat observed analysis).

Subgroup	Proportion with Response
Pretreatment HIV RNA <100,000 copies/mL	
Decline to <400	84%
Decline to <50	79%
Pretreatment HIV RNA >100,000 copies/mL	
Decline to <400	74%
Decline to <50	60%
Overall	
Decline to <400	79%
Decline to <50	67%

Based on data presented by Elion et al, 11th CROI, 2004.

explored potential reasons why some triple-nRTI regimens are not performing as would have been expected. Thirty-two of 37 patients had adequate minimum plasma concentrations of all 3 drugs at week 4. Analysis of intracellular nRTI triphosphate (the active metabolite) levels using direct liquid tandem mass spectroscopy was performed in 14 patients at week 4, including 1 patient in whom treatment was failing virologically. The triphosphate metabolite of at least 1 drug was found in all

patients and triphosphate metabolites of all 3 drugs were found in 8 patients. Therefore, this study did not provide full evidence that the poor virologic results were associated with reduced triphosphate levels.

Assessment of viral resistance suggested a major role of the combined K65R and M184V/I mutations in poor virologic outcomes. Genotypic analysis in 11 of the 12 patients with virologic failure (plasma HIV RNA never <400 copies/mL or a rebound of >0.7 log<sub>10</sub>

after suppression to below this level) showed the presence of the K65R plus M184V/I mutations in 9 patients (82%) and the M184V/I mutation alone in 2 patients. Among the 10 patients assessed with detectable HIV RNA levels but not virologic failure, 7 (70%) had the K65R plus M184V/I mutations, 2 had the M184V/I mutation alone, and 1 had wild-type virus. Changing treatment was successful in reducing HIV RNA levels to below 50 copies/mL in 14 patients with the K65R plus M184V/I mutations; some of the successful regimens were 4-drug regimens and many contained zidovudine. These data suggest that the failure noted among some triple-nRTI regimens may be due to rapid evolution of resistance rather than low plasma drug levels or poor intracellular processing of the drugs into active moieties.

The association of the K65R mutation with viral resistance and poor virologic response to these regimens receives support from an additional study examining the once-daily, 4-drug combination of abacavir/lamivudine/zidovudine/tenofovir (COL40263; Elion, 11th CROI, 2004). Although it might be expected that this abacavir/tenofovir-containing combination would also yield poor virologic outcomes, results of the study indicate otherwise. As shown in Table 1, 79% of the 56 patients studied had HIV RNA levels below 400 copies/mL and 67% had levels below 50 copies/mL at week 24.

Rates of early virologic response were better with the zidovudine-containing 4-drug regimen than with the abacavir/lamivudine/tenofovir regimen assessed in the TONUS study (ESS30009) among patients with baseline HIV RNA levels less than or greater than 100,000 copies/mL (Table 2). Baseline genotypic analysis showed that of isolates from 8 nonresponders to the 4-drug regimen, 1 had the K103N resistance mutation, 1 had a T215V/F reversion, and 6 had wild-type virus. Analysis of isolates from the 8 nonresponders at the last study visit (time of withdrawal from the study or last visit after 24 weeks) showed the K65R mutation in only 1 patient, 1 or more thymidine analogue mutations (TAMs) in 2 patients, and 1 or more TAMs plus the M184V/I mutation in 3 patients; 2 of the isolates were wild-type virus. These data

**Table 2.** Comparison of early HIV RNA response with abacavir/lamivudine/tenofovir in study ESS30009 and with abacavir/lamivudine/zidovudine/tenofovir in study COL40263. Based on early virologic nonresponse criteria used in ESS30009: (1) Less than 2-log copies/mL decline from baseline by week 8 and HIV RNA of 50 copies/mL or higher by week 8, and (2) 1-log copies/mL or greater increase above nadir at or before 8 weeks.

Subgroup	Early HIV RNA Response
Pretreatment HIV RNA <100,000 copies/mL	
ESS30009	56%
COL40263	83%
Pretreatment HIV RNA >100,000 copies/mL	
ESS30009	32%
COL40263	52%
Overall	
ESS30009	51%
COL40263	76%

Based on data presented by Elion et al, 11th CROI, 2004.

suggest a potential protective effect of zidovudine on the development of the K65R mutation.

An analysis by Parikh and colleagues (11th CROI, 2004) indicated that the prevalence of the K65R mutation in patients who have had genotypic testing increased from 0.4% in 1998 to 3.6% in 2003 and that the combined presence of the K65R and M184V/I mutations changes susceptibility to nRTIs compared with the presence of either mutation alone. As shown in Table 3, the combination of the 2 mutations reduces susceptibility to abacavir, didanosine, and lamivudine, but appears to result in hypersusceptibility to zidovudine. The effect of the K65R mutation on nRTI activity appears to be explained by a combination of decreased nRTI incorporation into viral DNA and decreased excision of the nRTI from the growing DNA chain, according to a study reported by White and colleagues (11th CROI, 2004). Decreased incorporation results in increased resistance, whereas decreased excision results in increased susceptibility, since the drug is not being removed as readily from the growing chain. The balance between these 2 competing effects results in the net susceptibility. This study showed that the presence of the next nucleotide to be added in the chain and its concentration both have an effect on excision efficiency, with higher concentrations of the next nucleotide resulting in reduced excision. Although most nRTIs experienced slightly decreased or no change in excision in the presence of K65R, zidovudine-monophosphate excision was dramatically decreased at physiologic concentrations of the next nucleotide. Overall, for most nRTIs, the K65R mutation acts to increase resistance by decreasing nRTI incorporation, with this effect being counterbalanced to varying degrees by the effect of the mutation in increasing the nRTI stability after incorporation (decreased excision). Virus with the K65R mutation may also have reduced replication capacity in association with reduced incorporation of the natural nucleotides. In the case of zidovudine, the increase in stability more than offsets the decreased incorporation, increasing the susceptibility of K65R virus to zidovudine compared

**Table 3. Effect of Reverse Transcriptase M184V and K65R Mutations on Susceptibility\* to Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors**

	<b>K65R</b>	<b>M184V</b>	<b>K65R + M184V</b>
<b>Abacavir</b>	4.2	2.8	11
<b>Didanosine</b>	2.7	1.8	3.4
<b>Lamivudine</b>	60	>100	>100
<b>Tenofovir</b>	2.4	0.4	1.0
<b>Zidovudine</b>	1.1	0.9	0.6

\*Expressed as fold change. Adapted from Parikh et al, 11th CROI, 2004.

with the established clinical cutoff value for the drug (Table 4). Susceptibility is preserved (ie, is below clinical cutoffs) for stavudine and abacavir, and susceptibility is reduced for tenofovir, didanosine, lamivudine, and zalcitabine.

It is known that TAMs reduce nRTI susceptibility by increasing nucleotide excision; the opposition of this effect to that of reverse transcriptase with the K65R mutation may help explain the relative lack of virus with both TAMs and the K65R mutations.

### Results of Other Initial Therapy Studies

#### Emtricitabine

Emtricitabine (formerly FTC) is a recently approved nRTI, which is very similar to lamivudine. The FTC-301A study compared the effects of once-daily emtricitabine and twice-daily stavudine each in combination with once-daily didanosine/efavirenz in 571 treatment-

naive patients (Saag et al, *JAMA*, 2004). The emtricitabine regimen was associated with a statistically significant higher rate of virologic response (<50 copies/mL) at 48 weeks (78% vs 59%). A recent report (Powderly, 11th CROI) on metabolic outcomes with the 2 regimens indicated that the stavudine-containing regimen was associated with more adverse effects in terms of body-fat loss and a substantially greater increase in fasting triglyceride levels than the emtricitabine regimen. The emtricitabine regimen was also associated with a significantly greater increase in high-density lipoprotein (HDL) cholesterol level.

#### Once-Daily Versus Twice-Daily Abacavir

Study CNA30021—which compared once-daily and twice-daily abacavir each combined with lamivudine/ efavirenz in 39 treatment-naive patients—indicated comparable virologic response rates

**Table 4. Effect of Reverse Transcriptase K65R Mutation on Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitor Binding and Incorporation, Stability, and Susceptibility**

	<b>Binding/ incorporation</b>	<b>Stability</b>	<b>Net susceptibility in cell culture (versus clinical cutoff)</b>
<b>Zidovudine</b>	↓	↑↑	Hypersusceptible
<b>Stavudine</b>	↓	—	Susceptible
<b>Tenofovir</b>	↓↓	↑ / —	Reduced susceptibility
<b>Didanosine</b>	↓↓	—	Reduced susceptibility
<b>Abacavir</b>	↓↓	↑	Susceptible

↓,↓↓ indicates decreased; ↑,↑↑, increased; —, no effect. Data from White et al, 11th CROI, 2004.

with the 2 regimens (Craig, 11th CROI, 2004). Although the group receiving twice-daily abacavir had a somewhat longer time to treatment response, plasma HIV RNA levels were at or below 50 copies/mL in both groups after approximately 25 weeks during the 48-week study.

### **CD4+ Cell Count Decline Despite Undetectable HIV RNA Level**

A retrospective analysis of data from 302 patients receiving antiretroviral regimens containing didanosine and tenofovir has provided a potential explanation for the observation of CD4+ cell count declines in patients with HIV RNA levels below assay detection limits (Negredo, 11th CROI, 2004). All patients in the analysis had HIV RNA levels below detection limits. Significant decreases in CD4+ cell, CD8+ cell, and total lymphocyte counts were observed only among those patients receiving both didanosine 400 mg and tenofovir 300 mg; approximately 50% of these patients had CD4+ cell count declines of more than 100/ $\mu$ L at 48 weeks. It is known that tenofovir acts to increase didanosine levels; didanosine levels in patients receiving the 400 mg dose were elevated during treatment and decreased significantly after didanosine dose reduction. Thus, the CD4+ cell count decline appears to be associated with lymphocyte toxicity from elevated didanosine levels rather than reduced virologic effect. The didanosine dose should be decreased to 250 mg when given in combination with tenofovir.

### **Once-Daily Versus Twice-Daily Lopinavir/Ritonavir**

A study comparing once-daily and twice-daily lopinavir/ritonavir, each with tenofovir/emtricitabine in 190 treatment-naive patients, showed little difference between the once-daily and twice-daily regimens in terms of treatment response (plasma viral load <50 copies/mL) at 48 weeks (Gathe, 11th CROI, 2004). Response rates were 70% in the once-daily group and 64% in the twice-daily group (difference, 6.4%; 95% confidence interval, -7.3% to 20.1%). Response rates with the PI-based regimens did not exceed 70%

when the data were analyzed on an intent-to-treat basis.

### **Boosted Atazanavir After Early Virologic Failure**

The BMS 045 trial compared atazanavir 300 mg/ritonavir 100mg; atazanavir 400 mg/saquinavir 1200 mg; and lopinavir 400 mg/ritonavir 100 mg, each combined with tenofovir and 1 nRTI in patients who had received 1 or 2 prior antiretroviral regimens. (De Jesus et al, 11th CROI, 2004) The atazanavir/ritonavir regimen was comparable to the lopinavir/ritonavir regimen in reducing plasma HIV RNA levels at 48 weeks (mean reductions of 1.93 log<sub>10</sub> and 1.87 log<sub>10</sub>, respectively). The reduction with atazanavir/saquinavir (1.55 log<sub>10</sub>) was not as great as with lopinavir/ritonavir (statistically significant in a time-averaged difference estimate). The ritonavir-boosted atazanavir regimen appears to provide better virologic activity than regimens with unboosted atazanavir. Further, the BMS045 study showed reductions in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels with both of the boosted atazanavir regimens, suggesting the potential for reduced metabolic adverse effects; however, HDL cholesterol also was reduced. Although the boosted atazanavir regimen has yet to be examined in a trial of initial therapy, these findings have prompted some practitioners to use ritonavir-boosted atazanavir when atazanavir is being used in initial antiretroviral regimens. The antiviral activity is likely to be similar in antiretroviral-naive patients treated with this regimen, but the absence of lipid effects still needs to be demonstrated in the treatment-naive population, since most of the patients evaluated in the BMS 045 study were coming off of a ritonavir-containing regimen.

### **Conclusion**

The timing and choice of the initial antiretroviral regimen continues to be refined. As discussed in the recently published 2004 guidelines on antiretroviral therapy by the International AIDS Society–USA panel (Yeni et al, *JAMA*, 2004), not much has changed in the

decision process of when to initiate therapy. On the other hand, optimal choices regarding the type of initial regimen to use are becoming clearer. Assuming equal potency, the choice of initial regimens should focus on the tolerability of the regimen, especially with regard to subtle, perhaps intermittent, intolerances that lead to missed doses. Once-daily dosing schedules and lower pill burden remain important considerations in the choice of initial therapy as well. In this regard, fixed-dose combinations of abacavir/lamivudine and tenofovir/emtricitabine have just been approved by the US Food and Drug Administration for once-daily administration.

Finally, recent studies demonstrate in full relief the importance of conducting clinical trials to fully elucidate the utility of newer treatment combinations. Very few investigators or clinicians predicted the poor responses noted among the tenofovir/abacavir or the didanosine/lamivudine/tenofovir combinations. Similarly, the potential protective effect of zidovudine on the appearance of the K65R mutation could only be fully established through carefully performed clinical trials. Although the data for the “best” regimen for initial therapy will continue to evolve, the ultimate “best regimen” is what is best for each individual patient and this remains a function of good physician-patient communication.

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