**When to Start Antiretroviral Therapy**

The question of when to initiate antiretroviral therapy has been a central controversy in HIV management for more than 15 years, yet there are limited data from randomized controlled trials addressing it. A major obstacle to performing such a study is the need for large numbers of asymptomatic, antiretroviral therapy–naïve individuals observed over years until death or a clinical event beginning from when their CD4+ cell counts are above 500/μL. Observational cohort studies with substantial person-years of follow-up have informed this debate in the absence of randomized trials. Emerging evidence regarding the damage caused by untreated HIV infection-related inflammation and immune activation at all stages of disease, and the benefits of modern antiretroviral therapy in preventing both AIDS- and non–AIDS-related morbidity and mortality has supported a return to starting treatment early. The NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) study compared long-term outcomes of immediate versus deferred therapy at 2 CD4+ cell count thresholds. Results showed a 94% increased risk of all-cause mortality when antiretroviral therapy was deferred at CD4+ cell counts greater than 500/μL. This article summarizes presentations made by Mari M. Kitahata, MD, MPH, at the International AIDS Society–USA continuing medical education programs held in November 2009 in New York City and in May 2010 in San Francisco. The original presentations are available as Webcasts at www.iassusa.org.

Although when to initiate antiretroviral therapy has been a principal question in HIV management, there are limited randomized trial data informing this debate. Recommendations for when to start treatment for asymptomatic patients have shifted back and forth since the introduction of combination antiretroviral therapy more than 15 years ago. Between 1998 and 2000, the US Department of Health and Human Services (DHHS) HIV treatment guidelines recommended that most patients be offered treatment, including those with asymptomatic disease and a CD4+ cell count greater than 500/μL (Panel on Antiretroviral Guidelines for Adults and Adolescents, DHHS, 2009) and in 2010 by the International AIDS Society–USA (Thompson et al, JAMA, 2010) recommend treatment for asymptomatic patients with CD4+ cell counts of 500/μL or less and consideration of treatment for those with counts greater than 500/μL. Greater awareness that HIV-associated inflammation and immune activation damage the immune system and end organs at every stage of disease has contributed to current recommendations, which state there is no CD4+ cell count at which initiating therapy is contraindicated and describe circumstances for which treatment is recommended regardless of CD4+ cell count. The approach of delaying potentially toxic medications as long as possible has shifted to an approach of initiating therapy as soon as possible. What data support this move back to earlier treatment?

**Randomized Controlled Clinical Trial Data**

Since the introduction of combination antiretroviral therapy, the only clinical trial that has randomly assigned asymptomatic, antiretroviral-naïve patients to initiate treatment or defer treatment is the CIPRA (Comprehensive International Program of Research on AIDS) HT 001 trial. This trial of patients with moderately advanced disease compared those who initiated antiretroviral therapy at CD4+ cell counts between 201/μL and 350/μL with patients who deferred treatment until their CD4+ cell count declined to the World Health Organization (WHO)-recommended treatment threshold of 200/μL or less. The trial was stopped early when interim analysis showed that deferral of therapy resulted in a 4-fold increase in mortality (P = .001) and a 2-fold increased risk of tuberculosis (P < .01) (Severe et al, N Engl J Med, 2010).

The SMART (Strategies for Management of Antiretroviral Therapy) trial was initially designed to study asymptomatic patients randomly assigned to initiate treatment or defer treatment, but inability to enroll sufficient numbers of treatment-naïve patients resulted in the conversion of this study to a continuous treatment versus intermittent treatment trial. However, a post hoc analysis of a subgroup of 477 subjects (9% of the participants in the SMART trial) who were treatment-naïve or had interrupted treatment for at least 6 months found that patients who deferred treatment until CD4+ cell counts fell below 250/μL had a 4-fold higher risk of AIDS- or non–AIDS-

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related event or death than subjects who (re)started antiretroviral therapy at CD4+ cell counts greater than 350/μL (P < .002) (SMART Study Group et al, J Infect Dis, 2008).

**Evidence Supporting Early Initiation of Antiretroviral Therapy**

Beyond these few data from randomized trials, a growing body of evidence that antiretroviral treatment can prevent irreversible damage to the immune system, as well as AIDS- and non-AIDS-related morbidity and mortality, supports earlier initiation of therapy. Untreated HIV infection results in early onset of immune system defects similar to those that occur in normal aging (Cao et al, JAIDS, 2009; Tenorio et al, Clin Immunol, 2009; Desquillbet et al, J Gerontol A Biol Sci Med Sci, 2007; Appay and Rowland-Jones, Trends Immunol, 2002).

Ongoing HIV replication and inflammation are associated with increased levels of proinflammatory cytokines, decreased capacity to renew T cells, and thymic and lymphoid fibrosis. These immune defects, referred to as immunosenescence, persist even after years of effective antiretroviral therapy, especially when treatment is started late in disease (Deeks and Phillips, BMJ, 2009; Kuller et al, PLoS Med, 2008; Gras et al, JAIDS, 2007; Moore and Keruly, Clin Infect Dis, 2007). T-cell senescence and proliferation defects persist even in treated HIV-infected individuals who maintain viral suppression, and they are associated with poor CD4+ T-cell recovery (Hunt et al, CROI, 2010).

These data demonstrate that there is no "asymptomatic" phase of HIV infection, as damage is observed at all stages of HIV disease. Levels of inflammatory markers that are associated with cardiovascular disease (CVD) and mortality—including high-sensitivity C reactive protein, interleukin-6, D-dimer, and cystatin-C—are markedly elevated in HIV-infected patients compared with noninfected subjects after adjustment for age, sex, and race (Neuhaus et al, J Infect Dis, 2010). HIV-mediated increases in T-cell activation play a central role in the pathogenesis of untreated HIV infection (Deeks et al, Blood, 2004) and are associated with a higher risk of disease progression and death (Li et al, J AIDS Hum Retrovir, 1998). Findings in the SCOPE (Study of the Consequences of the Protease Inhibitor Era) cohort showed that immune activation, measured as percentage of CD38+HLA-DR+CD8+ T cells, was substantially higher in untreated HIV-infected patients than in treated patients, as well as in treated HIV-infected patients compared with HIV-noninfected subjects (Hunt et al, J Infect Dis, 2003).

Despite successful therapy, patients initiating treatment at lower CD4+ cell counts have had longer exposure to HIV-associated inflammation and immune activation, resulting in greater immunosenescence, residual inflammation, and immune compromise than patients who initiate treatment at higher CD4+ cell counts (Deeks et al, BMJ, 2009). Factors known to limit CD4+ cell count recovery include older age (Gras et al, JAIDS, 2007), lower pretreatment CD4+ cell count nadir (Kelley et al, Clin Infect Dis, 2009; Moore and Keruly, Clin Infect Dis, 2007), high-level T-cell activation (Hunt et al, J Infect Dis, 2003), and lymphoid fibrosis (Schacker et al, AIDS, 2005).

In the CNICS (CPAR [Centers for AIDS Research] Network of Integrated Clinical Systems) cohort, Kelley and colleagues found that 40% of patients initiating antiretroviral therapy at a CD4+ cell count of less than 200/μL failed to achieve a count greater than 500/μL after 10 years of viral suppression (Kelley et al, Clin Infect Dis, 2009). Similarly, in the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort, estimated median CD4+ cell count response over 7 years of antiretroviral therapy was lower for patients initiating therapy at progressively lower CD4+ cell count strata (Gra et al, JAIDS, 2007). Furthermore, patients initiating antiretroviral therapy at less than 50 years of age had better responses than those initiating treatment at age 50 years or older in

![Figure 1. Median CD4+ cell count response over a period of 6 months to 7 years of antiretroviral therapy, according to CD4+ cell count at initiation of treatment (indicated by numbers at the right of the graph) in patients in the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort. Solid lines indicate patients younger than 50 years at treatment initiation; dashed lines, patients 50 years and older at treatment initiation. Adapted from Gras et al, JAIDS, 2007.](image-url)
each baseline CD4+ cell count stratum (Figure 1). Thus, immunosenescence associated both with untreated HIV infection and with normal aging limits the ability of antiretroviral therapy to restore CD4+ cell counts.

Initiating antiretroviral therapy at lower CD4+ cell counts is also associated with greater risk of virologic failure (eg, with a hazard ratio [HR] of 1.14 per 100/µL drop in CD4+ cell count at initiation in AIDS Clinical Trials Group [ACTG] 5124) (Kuller et al, *PLoS Med*, 2008; Riddler, *N Engl J Med*, 2008) and resistance to antiretroviral drugs when treatment is failing (Uy et al, *JAIDS*, 2009). Uy and colleagues found that patients with treatment failure who had initiated treatment at CD4+ cell counts of 350/µL or less had higher frequencies of resistance mutations to the drug classes to which they had been exposed than did patients with treatment failure who had initiated treatment at CD4+ cell counts greater than 350/µL (Uy et al, *JAIDS*, 2009).

Lower CD4+ cell counts are also associated with increased risk of non-AIDS-related morbidities often associated with aging, including cardiovascular, renal, and hepatic disease and non-AIDS-related malignancies. A number of cohort studies have found that lower on-therapy CD4+ cell count predicts an increased risk of non-AIDS-related events (Phillips et al, *AIDS*, 2008). Data from the HOPS (HIV Outpatient Study) cohort showed an 80% increased risk of new cardiovascular events among patients initiating antiretroviral therapy at CD4+ cell counts of less than 350/µL compared with those starting treatment at CD4+ cell counts of greater than 350/µL, after controlling for smoking, sex, and age (Lichtenstein et al, *IAC*, 2008).

The damage from untreated HIV infection and ongoing HIV replication to end organs is observed in patients with early HIV disease. Cohort studies have shown accelerated organ-system damage to renal, hepatic, cardiovascular, and neurocognitive systems that may be avoided by starting treatment earlier.

Additional arguments in favor of earlier initiation of antiretroviral therapy come from data showing that initiation at progressively higher CD4+ cell counts reduces risk of antiretroviral drug toxicities, including peripheral neuropathy, anemia, renal insufficiency, and lipodystrophy (Severe et al, *N Engl J Med*, 2010; Lichtenstein et al, *JAIDS*, 2008; Lichtenstein et al, *JAIDS*, 2003). Present therapeutic options are potent, durable, well tolerated, more forgiving of poor adherence, and safe. However, all potential long-term adverse effects are unknown.

Finally, despite dramatic reductions in mortality in the combination antiretroviral therapy era, higher mortality persists among patients treated with antiretroviral drugs than among age-matched, HIV-seronegative persons (Antiretroviral Therapy Cohort Collaboration [ART-CC], *Lancet*, 2008). Moreover, life expectancy is 10 years to 30 years less than that for uninfected patients depending on when treatment is started. For example, patients initiating antiretroviral therapy with CD4+ cell count nadirs of less than 100/µL, 100/µL to 200/µL, and greater than 200/µL have progressive increases in life expectancy of approximately 10 years at each stratum (ART-CC, *Lancet*, 2008). Mortality in HIV-seropositive persons has been found to approach that of HIV-seronegative persons only when CD4+ cell counts during antiretroviral therapy increase into the normal range (Lewden, *JAIDS*, 2007). Therefore, the most effective approach to preventing morbidity and mortality in HIV-infected individuals may be to initiate antiretroviral therapy before any measurable immunodeficiency has occurred (Jain and Deeks, *Curr HIV/AIDS Rep*, 2010).

**Observational Data**

Whether a randomized controlled trial or an observational study, a major challenge to investigating when to initiate antiretroviral therapy is the requirement for large numbers of antiretroviral-naive participants observed for many years to death or clinical event. As noted, despite intense debate since the introduction of combination antiretroviral therapy regarding when to initiate treatment for asymptomatic patients, only 1 such randomized clinical trial has been performed. This trial examined a CD4+ cell count threshold well below where the current debate is focused, made possible in part by the more rapid disease progression among patients with CD4+ cell counts of less than 200/µL.

The challenge posed by observing patients for many years to record sufficient clinical events is even greater for patients with CD4+ cell counts above 350/µL, and greater still for patients with counts above 500/µL. Thus, only a few observational studies have had sufficient person-years of follow-up and the methods to address this question. Studies using 3 different approaches to analyzing observational data have been cited in the debate on when to start antiretroviral therapy: (1) prognostic studies that observe only patients who initiate antiretroviral therapy, (2) prognostic studies that use imputation to estimate outcomes of deferring antiretroviral therapy, and (3) cohort studies that observe patients who initiate and patients who defer antiretroviral therapy.

Numerous observational studies have reported the prognosis for patients who initiated antiretroviral therapy at particular CD4+ cell count levels. However, prognostic studies cannot answer the question of when to initiate antiretroviral therapy because they lack patients who defer treatment with whom to compare survival. Moreover, most prognostic studies have examined only short-term outcomes. The relevant question is not whether patients survive 3 years to 5 years after initiating treatment, but whether delaying treatment decreases their long-term survival over many decades.

The second approach used in the ART-CC study examined prognostic data (ie, patients initiating antiretroviral therapy at a particular CD4+ cell count threshold) from cohorts primarily in Europe. As such, it lacked data for patients deferring treatment. Thus, the study was subject to lead-time bias because untreated patients who developed an AIDS-defining event or died before initiating treatment could not be included in the analysis. The authors used data from a separate patient population observed during the period...
1989 to 1995, when combination antiretroviral therapy was not available, to impute events that might have occurred in patients who would have deferred treatment in the current study. The adjusted risk of AIDS or death with deferral of therapy was compared to that in the ART-CC cohort in CD4+ cell count increments of 25/μL.

The results indicated an increase in the adjusted HR of AIDS or death in the deferred treatment group at progressively lower CD4+ cell counts. For example, deferral of treatment until the CD4+ cell count fell to 251/μL to 350/μL, compared with initiating therapy at a CD4+ cell count of 351/μL to 450/μL, was associated with a 28% increase in the HR of AIDS or death (adjusted HR, 1.28; 95% confidence interval [CI], 1.04–1.57) (When to Start Consortium et al, Lancet, 2009). However, the HR for deferral of therapy until a CD4+ cell count between 501/μL and 400/μL, compared with initiation of therapy at a count between 401/μL and 500/μL, was not statistically significant (adjusted HR, 1.09; 95% CI, 0.85–1.38).

Methodologic concerns raised by this study include the likelihood that rates of AIDS-defining events and mortality in earlier years of the epidemic differ from those in the modern treatment era, particularly with regard to non-AIDS-related events, which are not included in this analysis. As discussed above, data suggest that benefits of very early treatment initiation include preventing non-AIDS-related morbidity and mortality. In addition, this study did not include patients with CD4+ cell counts higher than 550/μL, in contrast to the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) study discussed below.

The third approach to analyzing observational data is the cohort method used in the NA-ACCORD study, which observed individuals who initiated and those who deferred treatment beginning at the same CD4+ cell count level. The NA-ACCORD study is a collaboration involving more than 60 geographic areas and more than 110,000 persons with HIV infection. The authors defined a protocol similar to a randomized clinical trial of antiretroviral-naive individuals with no prior AIDS-defining events. Patients were enrolled between 1996 and 2006 and observed from the time of their first CD4+ cell count in one of 2 strata (350/μL to 500/μL and more than 500/μL).

Subjects who entered the cohort with a CD4+ cell count in these ranges and initiated therapy within the next 6 months (immediate-treatment group) were compared with those who deferred therapy until their CD4+ cell counts fell below a predefined threshold of less than 350/μL or less than 500/μL (deferred-treatment group). As in a randomized trial, not all patients in the deferred group transitioned to CD4+ cell counts below the threshold and initiated therapy, referred to in randomized trials as protocol violations. However, also as in a randomized trial, omitting patients with protocol violations from the analysis introduces selection bias. Therefore, multivariate Cox regression with time-dependent inverse probability weights was used to adjust for the censoring analogous to protocol violations of randomized trials. Analysis of 9555 patients with CD4+ cell counts greater than 500/μL (median CD4+ cell count, 664/μL; interquartile range, 573/μL–811/μL) yielded a follow-up of 26,439 person-years, and data were stratified by cohort and calendar year. The size and duration of this study allowed the use of death alone as the endpoint, a more definitive and all-inclusive outcome measure.

Results demonstrated that deferral of therapy at CD4+ cell counts greater than 500/μL was associated with a 94% increased risk of all-cause mortality (adjusted HR, 1.94; 95% CI, 1.37–2.79), as shown in Figure 2 (Kitahata et al, N Engl J Med, 2009). This increased risk held steady across the 10-year period of the study. Older age, HCV infection, and injection drug use were independent predictors of mortality, largely due to non-AIDS-related events for the subset with known cause of death.

As with any observational study, even after adjustment for factors known to predict mortality, residual confounding may occur because of unmeasured factors (eg, behavioral factors) that may affect survival. However, sensitivity analyses of the NA-ACCORD data consistently showed increased risk of death with deferral of treatment and that the size of unmeasured confounding would have to be uncommonly large to mitigate the results of this study.

Conclusion

Data from randomized controlled trials could provide definitive answers to questions regarding when to initiate antiretroviral therapy. However, there are numerous obstacles to performing such trials, including the difficulty of enrolling sufficient numbers of antiretroviral-naive patients with CD4+ cell counts greater than 500/μL and observing them long enough to accrue sufficient endpoints to achieve adequate statistical power. In addition, findings may be less relevant by 2015 or later, given the rapid pace at which knowledge about HIV advances.

Practitioners, investigators, and patients may find the available data indicating substantial benefit of very early initiation of antiretroviral therapy compelling enough to outweigh the risks of antiretroviral medications. With regard
to the greater exposure to potential long-term drug toxicities with earlier initiation, it is instructive to consider that earlier initiation does not constitute a large increase in overall exposure to therapy when taken in the context of a lifetime of treatment. For example, assuming an annual CD4+ cell count loss of approximately 80/μL, initiating treatment at a CD4+ cell count of 550/μL instead of 350/μL would add approximately 2.5 years of treatment duration. For a 25-year-old, HIV-infected individual, assuming lifelong treatment of at least 40 years, this would add only 7% of treatment duration over the patient’s lifetime (PA Volberding, MD; oral communication, May 2010). US antiretroviral treatment guidelines agree that evidence supports early initiation of treatment in asymptomatic HIV-infected patients.

Portions presented by Dr Kitahata in November 2009 and May 2010. First draft prepared from transcripts by Matthew Stenger. Revised and updated by Dr Kitahata in September 2010.

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Suggested Reading


Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm³ or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm³ or greater. JAIDS. 2007;45:183-192.


Lichtenstein KA, Armon C, Buchacz K, et al. Initiation of antiretroviral therapy at CD4 cell counts >1 = 350 cells/mm³ does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency. JAIDS. 2008;47:27-35.


and in those not receiving ART at baseline in the SMART study. J Infect Dis. 2008;197:1135-1144.


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