When to Start Antiretroviral Therapy? NA-ACCORD Stimulates the Debate

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By AIDS Reader [1]

One of the most highly discussed and publicized HIV-related presentations at the recent Interscience Conference on Antimicrobial Agents and Chemotherapy/Infectious Diseases Society of America (ICAAC/IDSA) joint meeting was the study from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a collaboration of 22 North American prospective clinical cohorts, examining the question of when to start therapy.¹ The NA-ACCORD analysis presented by Kitahata and colleagues included more than 8000 patients (with almost 25,000 person-years of follow-up) who had CD4⁺ cell counts between 350/μL and 500/μL at a clinic visit between 1996 and 2006. The study compared all-cause mortality between those who started antiretroviral therapy within 1.5 years of their first CD4 count within that range (the "immediate" group) and those who did not start therapy within 1.5 years of reaching this CD4 threshold (the "deferred" group). The investigators found a 70% greater mortality in the deferred group (hazard ratio [HR] 1.7; P < .001), which was comparable to the effect of being 10 years older (HR 1.6; P < .001).

As with any observational cohort study, there is a potential for selection bias. For patients in the immediate group, therapy may have been started when they had high CD4 counts because they were motivated, were predicted to be adherent to treatment, or had no concurrent conditions that might have complicated antiretroviral therapy, whereas those in the deferred group may have been less adherent or had characteristics that could have increased the risk of mortality irrespective of antiretroviral therapy, such as injection drug use or coinfection. However, the survival advantage of early therapy persisted after adjusting for injection drug use and hepatitis C virus coinfection. In addition, rates of viral suppression for patients receiving antiretroviral therapy were comparable in the immediate and deferred groups, suggesting that adherence differences did not account for the study’s findings.

Another form of bias common to observational cohort studies is lead time bias, in which events that occur before the initiation of therapy are not captured. One of the strengths of the NA-ACCORD study is that data collection for this cohort started from the same CD4 threshold for both groups, so that deaths occurring before the initiation of therapy in the deferred group are included in the analysis. In this sense, the NA-ACCORD investigators have the capability to mimic a clinical trial in which patients are randomized to immediate or deferred therapy. At the conclusion of her presentation, Kitahata announced that a similar analysis looking at the initiation of antiretroviral therapy at CD4⁺ cell counts above 500/μL is being performed. These data are to be presented at this year’s Conference on Retroviruses and Opportunistic Infections in Montreal in February.

Where do the NA-ACCORD results leave us as HIV care providers in determining when to start therapy? It’s important to note that although this study is unique in several ways, its findings do not stand in isolation and are consistent with those of other large cohort studies, including the Antiretroviral Therapy (ART) Cohort Collaboration,² Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE),³ Aquitaine,⁴ and others,⁵⁻⁸ which have demonstrated lower mortality, morbidity, and drug toxicity and/or improved CD4 counts with the initiation of therapy at CD4⁺ cell counts above 350/μL. The consistency of the data is striking; the only drawback is the observational nature of the studies. Still, there is precedent for using observational data to establish guidelines. For example, the most recent version of both the Department of Health and Human Services (DHHS) and the International AIDS Society–USA (IAS-USA) guidelines used observational studies to revise their CD4 thresholds for the initiation of therapy to CD4⁺ cell counts of 350/μL.⁹,¹⁰ Assuming the results of the NA-ACCORD study are published in a peer-reviewed journal, following a closer review of the study’s statistical methodology, these findings will then be considered by...
treatment guideline committees in the context of previously published observational studies. The closest thing we have to a clinical trial that compares immediate with deferred therapy in the HAART era is a post hoc subset analysis of the Strategies for Management of Antiretroviral Therapy (SMART) study, which looked at participants who were not receiving therapy at enrollment because either they were treatment-naive or they had interrupted therapy. In the analysis, patients who deferred therapy until their CD4+ cell counts had fallen to below 250/μL had a 4-fold increase in fatal and nonfatal AIDS-defining and serious non–AIDS-defining events compared with those who started therapy immediately. What keeps this study from being definitive, however, is the relatively small sample size (N = 477) and the heterogeneous population (not all were treatment-naive).

The International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) has designed and planned a large clinical trial—the Strategic Timing of AntiRetroviral Treatment (START) trial—that will randomize treatment-naive patients who have CD4+ cell counts above 500/μL either to initiate therapy immediately or to wait until the CD4+ cell count has fallen below 350/μL. HIV experts are divided over whether such a trial is feasible, valuable, or ethical. The argument in favor of the trial is obvious: Can we rely only on nonrandomized, observational data to make such an important treatment decision, and one that has such enormous cost implications? Arguments against the trial include (a) the difficulty of finding enough treatment-naive patients who have high CD4 counts and are willing to be enrolled in a trial that might result in their being treated either "too early" or "too late" (b) the expected high cost of such a study; and (c) the possibility that during the course of this multiyear trial, data supporting early therapy will become compelling enough to change treatment standards and guidelines, making enrollment into the trial impossible or unethical and rendering the question that the study was designed to answer obsolete.

Current guidelines recommend treatment for all patients with CD4+ cell counts below 350/μL. However, in contrast to previous treatment recommendations by guideline committees, there is no longer a "do not treat" category. Instead, guidelines point out that the exact CD4+ cell count above the current 350/μL threshold at which treatment should be initiated is not known and that there are patients who should be treated or considered for treatment regardless of their CD4 count. Other indications for therapy, at least in some of the guidelines used in developed countries, include the presence of HIV-associated nephropathy, hepatitis B or C, pregnancy, high viral load, rapid CD4 count decline, high risk of cardiovascular disease, low CD4 percentage, and age above 55 years. Finally, current guidelines leave the door open for using antiretroviral therapy to reduce viral transmission (eg, for HIV-infected patients with seronegative partners). This approach was recently highlighted by a paper that used mathematic modeling to predict that annual universal testing and immediate initiation of therapy could dramatically reduce transmission and alter the course of the epidemic.

The decision to start therapy has always involved weighing the risks and benefits of therapy. It is to be expected that there would be benefits to starting therapy at higher CD4 counts—perhaps even at the very earliest stages of disease. We now know that the risks of HIV infection are not just those of immunosuppression and the resulting opportunistic infections and malignancies. There is growing interest in the effects of HIV infection on inflammation and immune activation, which have been shown to be present from the onset of infection.

Many of the cohort studies discussed above have found that HIV infection is associated with a greater risk of conditions not traditionally associated with HIV infection, such as cardiovascular disease, liver disease, and non–AIDS-defining malignancies. However, the marginal benefit of early antiretroviral therapy is smaller and harder to demonstrate than it is at lower CD4 counts, and at some point either the risks of therapy may outweigh the benefits or therapy may not be cost-effective. What allows us to consider early therapy now is not only the growing evidence of benefit but also the declining risks of therapy. Antiretroviral therapy today is more effective, better tolerated, less toxic, more convenient, and more forgiving of imperfect adherence than drug regimens used in the early years of the HAART era. In addition, the availability of second-generation agents and of drugs in new classes offers multiple sequencing steps for patients whose early lines of therapy still fail.

It may not be long before the more relevant question becomes "When not to start?" At that point, treatment may be offered to anyone ready and willing to be treated, regardless of CD4 count or viral load. If this happens, it will be based either on the results of trials like the START study or on accumulating observational data. In the meantime, we need to focus on 2 issues that may ultimately be more important than fine-tuning indications for therapy: (1) increasing early diagnosis by implementing CDC recommendations for routine voluntary testing; and (2) making sure there are resources, both human and fiscal, to provide care for the growing number of persons who will need
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HIV therapy.

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