EDITORIALS

When to Start Antiretroviral Therapy — Ready When You Are?

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The optimal time to start antiretroviral therapy in asymptomatic patients has been one of the central controversies in the care of patients with the human immunodeficiency virus (HIV) since the introduction of the first antiretroviral agent, zidovudine, more than two decades ago.[1] Since then, periods of enthusiasm for aggressive early intervention[2] have been followed by a more cautious approach.[3] This slowly swinging pendulum has been pushed back and forth by the extraordinary benefits of antiretroviral therapy on one side[4] and emerging data on its adverse effects on the other.[5]

The absence of a controlled, prospective study comparing early and deferred therapy has forced treatment guidelines to rely largely on data from observational cohort studies.[6,7] Currently, these guidelines state that the optimal time to start therapy for an asymptomatic patient with a CD4+ count of more than 350 cells per cubic millimeter is unknown.

In this issue of the *Journal*, Kitahata and colleagues present data from the one of the largest of these observational cohorts, the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).[8] The combined effort of 22 North American prospective research groups, NA-ACCORD evaluated patients with HIV infection who had not undergone previous therapy and who were stratified according to their CD4+ count at baseline: 351 to 500 cells per cubic millimeter or more than 500 cells per cubic millimeter. The investigators compared survival between patients who started antiretroviral therapy within the given CD4+ stratum with those who waited until after the CD4+ count fell below the stratum.

The results are striking. Among the 8362 patients with a CD4+ count of 351 to 500 cells per cubic millimeter, deferral of therapy until the CD4+ count had fallen to 350 cells or less was associated with an increase of 69% in the risk of death, as compared with patients who initiated therapy when their CD4+ count was within the designated range. Similarly, among the 9155 patients with a CD4+ count of more than 500 cells per cubic millimeter, deferral of therapy until the CD4+ count fell below 500 cells was associated with a significantly increased risk of death of 94%.

The strengths of this study included its relatively large size, the use of advanced statistical methods that attempted to analyze the data in a fashion similar to that of a randomized trial, and the use of survival (rather than AIDS progression or death) as the end point. The use of death from any cause is important in evaluating patients who have higher CD4+ counts, since HIV-related opportunistic infections and cancers develop relatively infrequently in such patients.[9] Indeed, in the NA-ACCORD study, the majority of deaths for which cause was available were from "non–AIDS-defining" causes. An additional strength of the study was its ability to minimize lead-time bias by having access to data for patients before antiretroviral therapy was started. In many other cohort studies, such events are either not accounted for[10] or must be estimated with the use of historical data.[11]

The strengths of the study notwithstanding, the results of the NA-ACCORD study cannot be considered definitive evidence that everyone with HIV should start receiving antiretroviral therapy. This was not a randomized trial, and the patients who chose to begin therapy early might have differed in other important ways from those who chose to defer therapy — ways that improved

survival but were not measured. Although NA-ACCORD investigators tried to account for this potential bias by controlling for known associations with an increased risk of death in patients with HIV infection (e.g., increased rates of coinfection with hepatitis C virus and of injection-drug use), some unmeasured factors inevitably remain. For example, in many ways, patients who were offered and began potent combination antiretroviral therapy with a high CD4+ count in the late 1990s were the ideal patients: highly adherent, committed to doing whatever they could to prevent AIDS, and willing to push through the sometimes punishing side effects and drug-regimen burdens of the early therapies. This sort of "health-seeking" behavior cannot be measured in the NA-ACCORD study yet could still substantially influence outcomes; its effects can be accounted for only in a randomized, prospective study. In addition to differences in baseline factors, such as HCV infection and injection-drug use, the rates of virologic suppression after 12 months of therapy differed between the two groups among patients with a CD4+ count of more than 500 cells per cubic millimeter (81% in the early-therapy group vs. 71% in the deferred-therapy group), which suggests different levels of adherence to therapy.

Some additional limitations should be considered. A relatively high proportion (approximately 45%) of patients in each study-specified stratum of CD4+ counts either did not initiate antiretroviral therapy or did not have a decline in the CD4+ count. These patients are not included in the comparative analysis, and we have no way of knowing whether antiretroviral therapy would have been beneficial in this group. Broader use of antiretroviral agents may increase the incidence of viral resistance. However, since data regarding resistance are unavailable at this time, we do not know how an earlier starting strategy would influence future treatment options. Data on certain toxic effects of antiretroviral therapy (most notably, metabolic and morphologic side effects) are not provided, and potential long-term toxicity cannot be addressed. The causes of death are available for only 16% of the patients who died; it will be important to obtain more complete follow-up on these patients to better understand the deleterious effects of poorly controlled HIV infection on end-organ dysfunction. It also must be determined whether some of the deaths might have been related to underlying differences (including lifestyle choices) between the two nonrandomized study groups.

Finally, the specific therapies that patients underwent reflected an earlier era in HIV therapy (the median year for starting treatment in these patients was 2000), so a high proportion of patients began regimens containing an unboosted protease inhibitor, a strategy that is no longer recommended, in part because of reduced efficacy in patients with more advanced HIV infection. Conversely, one could argue that the results of the NA-ACCORD study are all the more remarkable, given the numerous improvements in treatment since that time.

Even with the above limitations, the NA-ACCORD study adds to a growing body of data supporting earlier treatment for HIV infection. The Strategies for Management of Antiretroviral Therapy (SMART) trial (ClinicalTrials.gov number, NCT00027352) showed that continuous antiretroviral therapy was safer than intermittent antiretroviral therapy; this was true even among patients who had a CD4+ count of more than 350 cells per cubic millimeter but who were not receiving antiretroviral therapy at baseline. Therefore, in some ways, the SMART trial mimicked a study of early versus deferred therapy.[12] Another critical observation of the SMART trial was that non-AIDS complications occurred more commonly in patients in the intermittent-therapy group, which suggests that whatever the side effects of antiretroviral therapy, they were not as deleterious as untreated HIV infection.[13]

Potential additional benefits of earlier therapy for HIV may include a lower rate of drug-specific toxic effects, a greater likelihood of achieving a normal CD4+ count, a reduction in immune activation and inflammation, and a decreased risk of HIV transmission. Analyses of cost-effectiveness have shown that antiretroviral therapy also compares favorably with other widely adopted medical interventions.[4] Increasing the CD4+ threshold to start therapy at a range of 350 to 500 cells per cubic millimeter would add only a few years of additional therapy onto projected decades of treatment and hence generate a relatively small added lifetime cost. The impending availability of a greater number of generic antiretroviral drugs, including lamivudine in 2010, could further reduce the cost of treatment.

As we learned regarding the use of estrogen in postmenopausal women,[14] we must be cautious

in interpreting observational data despite efforts to control for confounding. The NA-ACCORD data do not provide definitive proof that we should be starting antiretroviral therapy in all patients with HIV infection. Such a conclusion would require data from a randomized, prospective clinical trial, and at least three such studies are either ongoing or planned. However, the supportive evidence for the benefits of earlier therapy continues to increase, making strategies to identify patients with HIV infection before the onset of substantial immunodeficiency all the more compelling.[15]

Five years ago, if an asymptomatic patient with HIV infection and a CD4+ count of more than 500 cells per cubic millimeter wished to start antiretroviral therapy, most experienced clinicians could have made an excellent case why treatment should be deferred. Today, if a similar patient were eager to start, we should be ready and willing to prescribe therapy — with ongoing careful monitoring of toxic effects that could arise during decades of treatment.

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A Step Forward in Therapy for Hepatitis C

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The therapy of hepatitis C began almost 25 years ago with a small trial of recombinant human interferon alfa.[1] The rationale for using interferon was its broad antiviral effects and the suspicion that it might be active against the still-undiscovered agent of non-A, non-B hepatitis. Indeed, interferon had striking effects, lowering serum aminotransferase levels and, in a proportion of patients, inducing a lasting improvement in serum enzyme levels. Not until the discovery of the hepatitis C virus (HCV) were the effects of interferon understood; treatment resulted in a decrease in HCV RNA levels, which led to a sustained absence of virus in a proportion of patients.[2] The difficulty was that interferon required parenteral injections, had multiple adverse effects, and resulted in a poor overall response rate. Nevertheless, interferon was approved for use for hepatitis C treatment in the United States in 1992.

The second important advance in hepatitis C therapy came with the use of ribavirin. Ribavirin is a nucleoside analogue known to have activity