

Early Antiretroviral Therapy for HIV Associated with Improved Survival

Kitahata MM, Gange SJ, Abraham AG, et al; NA-ACCORD Investigators. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;360:1815–26.

Study Overview

Objective. To determine the optimal time for initiation of antiretroviral therapy (ART) for HIV.

Design. Retrospective cohort study, with data collected from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the International Epidemiologic Databases to Evaluate AIDS project.

Setting and participants. Asymptomatic patients who had received medical care between 1996 and 2005, had never been treated with ART, and had no AIDS-defining illness were selected from a group of 67,527 HIV-infected patients enrolled in a cohort study in 22 research centers across 60 sites across the United States and Canada. 17,517 patients were stratified into 2 separate samples defined by a baseline CD4+ count (first group [$n = 8362$], CD4+ count of 351–500 cells/mm³; second group [$n = 9155$], CD4+ count ≥ 500 cells/mm³). Data were collected on demographic and behavioral characteristics, serial CD4+ counts, and timing of initiation of ART, and patients were linked to U.S. national and Canadian provincial death indexes. Early initiation of therapy was defined as the commencement of ART within 6 months after the baseline CD4+ count measurement and within the range of interest (351–500 cells/mm³ or > 500 cells/mm³, depending on the sample), if the CD4+ count remained in the baseline range. Deferred therapy was defined as therapy starting more than 6 months after enrollment once the CD4+ count dropped below the threshold for the group (either ≤ 350 or ≤ 500 cells/mm³, depending on the sample). Pre-specified subgroup analyses were conducted for patients with data on hepatitis C virus (HCV) infection or injection drug use and for those with data on HIV RNA.

Main outcome measures. Death from any cause, determined using multivariable Cox proportional hazards analyses conducted separately for each sample of patients. Covariates included sex, age at enrollment, infection with HCV, history of injection drug use, year of enrollment, CD4+ count at baseline, and baseline HIV RNA measurements. A sensitiv-

ity analysis was conducted to measure the possible effect of unmeasured confounding.

Main results. Patients in the early therapy group were older and more likely to be white. In the subgroup with relevant data, patients in the deferred therapy group were more likely to have HCV or a history of injection drug use.

Of 8362 patients with a CD4+ count of 351 to 500 cells/mm³, 2084 (25%) started ART within 6 months while their CD4+ count remained in the range of interest. Of 6278 patients who deferred therapy, 3449 transitioned to a CD4+ count of less than 350 cells/mm³ (803 of these began therapy), while the remaining 2829 had CD4+ counts that stayed in the initial range. Compared with early therapy, the relative risk of death for patients who deferred therapy was 1.69 (95% confidence interval [CI], 1.26–2.26; $P < 0.001$) after stratifying for year of first CD4+ count. Results remained significant after controlling for sex, age, baseline CD4+ count, and HCV status. Subgroups analyses showed that results were consistent after controlling for HIV RNA (for patients who had measured HIV RNA at baseline) and after excluding patients with a history of injection drug use or HCV infection and those who did not have data collected on these variables (1 center did not collect data on HCV or injection drug use). Among those with data available for injection drug use, the risk of death was attenuated when history of injection drug use was included as a covariate (relative risk, 1.28 [95% CI, 0.85–1.93; $P = 0.23$]).

In the second sample, results were similar. Of 9155 patients with a CD4+ count greater than 500 cells/mm³, 2220 (24%) started ART within 6 months after their first CD4+ count remained in the range of interest. Of the 6935 patients who deferred therapy, 3881 transitioned to a CD4+ count less than 500 cells/mm³ and 539 of these patients started ART. Compared with early therapy, the relative risk of death for patients who deferred therapy was 1.94 (95% CI, 1.37–2.79; $P < 0.001$). These results were consistent in all subgroup analyses.

In both samples, the risk of death was not associated with race or baseline HIV RNA level. Female sex was associated with an increased risk of death in both samples, but this increased risk diminished after adjusting for HIV RNA level, a

history of injection drug use, or presence of HCV infection. HCV infection and a history of injection drug use were associated with an increased risk of death. Most deaths in the study were from non-HIV-related illnesses.

Conclusion. Deferred ART was associated with an increased risk of death from any cause.

Commentary

The appropriate timing for initiation of ART has been a critically important but unresolved question in HIV therapy. Current guidelines use a CD4+ count of less than 350 cells/mm³ as the threshold for starting therapy in asymptomatic patients [1,2]. Treatment of patients at higher CD4+ counts has been proposed as an option upon consideration of the risk and benefit of early therapy. Potential benefits of early treatment are decreased transmission of HIV, a reduction in some HIV-related complications, and prevention of irreversible damage to the immune system, which might occur even at CD4+ counts above 350 cells/mm³ [1–4]. HIV also can increase the risk of non-AIDS-related malignancies as well as liver, renal, and cardiovascular disease, and early treatment might mitigate this risk [5–7]. Yet, early treatment comes with risks, including the toxicities of treatment and the risk for developing resistance if patients are noncompliant or if a sustained virologic response is unattainable [1,2].

Prior studies have demonstrated some benefit of starting therapy at higher CD4+ counts, although these studies have often used combined endpoints (progression to AIDS and death) or have not had adequate control groups to allow comparison with HIV-infected patients who deferred therapy [8,9]. In this study, Kitahata et al utilize a large cohort of HIV-infected, ART-naïve patients to assess differences in mortality between patients treated at higher CD4+ counts compared with patients treated later in the course of the disease. The results of this study are compelling because of the effect size—a 69% and 94% reduction in mortality in patients with a CD4+ count of 351 to 500 cells/mm³ and greater than 500 cells/mm³, respectively. The robust risk reductions in mortality persist even after controlling for other risk factors for death in HIV patients. Although the benefit of early therapy was attenuated in a subgroup analysis of patients with a starting CD4+ count of 351 to 500 cells/mm³ after controlling for injection drug use, the results show a consistent mortality reduction with early therapy. No such attenuation was evident in the subgroup analyses for patients starting ART with a CD4+ count greater than 500 cells/mm³.

This study has several limitations, most of which are related to the limitations of observational data. First, clear differences were present between the early and deferred therapy groups. Despite controlling for the primary differences, the number of covariates available to analyze was somewhat limited. The

authors performed a sensitivity analysis to measure the hypothetical influence of an unmeasured confounding variable on the results and showed that it would take a variable with an unusually large effect on mortality and large association with the decision for early versus deferred therapy to attenuate the results. However, multiple unmeasured confounding is possible and could certainly impact results. Second, at least 1 of the centers failed to collect data on injection drug use and HCV, both of which are clearly associated with mortality in HIV-infected patients. Excluding patients with limited data did not alter results, however. Third, limited data on cause-specific mortality were available, and information on medication toxicity and the reasons for early versus deferred therapy are unknown (a large number of patients in the sample with a CD4+ count of 351–500 cells/mm³ were not treated when their CD4+ count dropped below 350 cells/mm³, the current standard level for starting therapy).

Only a randomized trial can truly determine the appropriate CD4+ level to commence therapy, and several of these trials are in the works [10]. Yet, the data from this study could reasonably alter current guideline recommendations. Studies reporting incomplete immune reconstitution if starting therapy at lower CD4+ counts as well as the availability of improved treatments that decrease toxicities are also compelling reasons for early treatment [3,4]. As the editorial that accompanies this study suggests, this study should at least compel physicians to have fully informed discussions with their patients about the risk and benefits of starting ART at CD4+ counts above 350 cells/mm³.

Applications for Clinical Practice

Early initiation of ART is associated with decreased all-cause mortality in HIV-infected patients who have a baseline CD4+ count of 351 cells/mm³ or greater. Randomized controlled trials should help determine the appropriate threshold to start therapy. Physicians treating HIV-infected patients should discuss the role of early therapy with their patients.

—Review by Jason P. Block, MD, MPH

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