

CORRESPONDENCE



Early versus Deferred Antiretroviral Therapy for HIV

TO THE EDITOR: Kitahata et al. (April 30 issue)¹ addressed the question of whether persons who received antiretroviral therapy during their study lived longer if that treatment was initiated early rather than deferred. Through careful selection and censoring of patients in various subgroups, the authors attempted to eliminate a variety of sources of bias.

However, in censoring patients who did not start antiretroviral therapy during follow-up, they have selectively eliminated from the deferred-therapy group, but not the early-therapy group, those patients in whom disease progression was relatively slow. This introduces potential bias when addressing the related question of when to initiate antiretroviral therapy for all patients with high CD4+ counts, for whom the timing of disease progression is unknown.

The number of patients eliminated from the analysis because of slower disease progression exceeds the numbers in each early-therapy group. As stated in the accompanying editorial,² this study does not fully address the appropriate course of action for this sizable subgroup. Clinicians should take this information into account when counsel-

ing patients with high CD4+ counts about the appropriate timing for initiation of antiretroviral therapy.

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1. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;360:1815-26.
2. Sax PE, Baden LR. When to start antiretroviral therapy — ready when you are? *N Engl J Med* 2009;360:1897-9.

TO THE EDITOR: In one of two analyses conducted, Kitahata et al. used observational data to emulate a trial of early versus deferred antiretroviral therapy in patients infected with the human immunodeficiency virus (HIV) whose baseline CD4+ count was more than 500 cells per cubic millimeter. They used a previously developed methodology,¹ but their implementation of it was problematic.

Specifically, patients who initiated antiretroviral therapy within 6 months after baseline and whose CD4+ count remained above 500 cells per cubic millimeter until initiation were included in the early group. Patients who either died untreated or who initiated antiretroviral therapy with a CD4+ cell count of more than 500 cells per cubic millimeter within 6 months after baseline were included in the deferred group. This implementation effectively places patients with a better prognosis in the early group, possibly resulting in an exaggeration of the estimated benefit of early initiation.

In addition to contributing to potential bias, this implementation has the effect of producing comparison groups that do not correspond to

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meaningful clinical strategies regarding the optimal CD4+ cell count at which to initiate antiretroviral therapy.

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1. Hernán MA, Lanoy E, Costagliola D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. *Basic Clin Pharmacol Toxicol* 2006;98:237-42.

TO THE EDITOR: The authors acknowledge that unmeasured confounding factors may have played a role in their findings, and the accompanying editorial summarizes many potential confounders, such as “health-seeking” behavior. One additional factor deserves mention. A substantial subgroup of patients with HIV infection did not receive state-of-the-art care because of addiction, coexisting psychiatric conditions, illegal or underinsured status, or other socioeconomic problems. Confounding by indication is probable since this last subgroup is also far more likely to delay the start of antiretroviral therapy. The mortality within this underprivileged subgroup is high owing to causes such as suicide, violence, and illicit-drug intoxication. These causes of death even explain more than 30% of the total mortality among the patients with HIV infection in our center (1500 patients in care, with 11 of 36 deaths due to these causes in a 2-year period).

In light of the conflicting data coming from both sides of the Atlantic, and a health care insurance system undergoing reform in the United States, we really do need the randomized clinical trial data before drawing any firm conclusions.^{1,2}

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1. When To Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009;373:1352-63.
2. Simms C. Inequalities in the American health-care system. *Lancet* 2009;373:1252.

TO THE EDITOR: In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study, the majority of deaths were due to non-AIDS-defining conditions (hepatic, renal, cardiovascular, and non-AIDS cancers). Inves-

tigators should provide data on the prevalence of critical risk factors for death from these causes — smoking, alcoholism, hypertension, diabetes, coronary artery disease, renal insufficiency, and coinfection with hepatitis B virus — and the proportion of patients who used medications to treat these common coexisting conditions. As it happened with coinfection with hepatitis C virus, patients with these risk factors were probably less likely to start early antiretroviral treatment during the study period. Until the combined effects (presumably very important) of these risk factors on mortality are analyzed and controlled for, the authors cannot rule out the possibility that the observed benefit of earlier antiretroviral treatment was related to the fact that the early-therapy group had a lower baseline prevalence of risk factors for non-AIDS conditions as compared with the deferred-therapy group.

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THE AUTHORS REPLY: These letters highlight some of the choices that need to be made regarding both how the question of when to start antiretroviral therapy is formulated and how different subgroups, such as patients with slow or fast disease progression, should be addressed in the analysis.

In response to Buchbinder and Jain: we note that patients whose CD4+ counts remain in the target window but who do not initiate therapy are not censored — they remain at risk of death in the analysis and are subject only to what we call outside-of-protocol censoring. However, if we eliminate this censoring altogether, our inferences for the risk of death with deferral for the first analysis (CD4+ count of 350 to 500 cells per cubic millimeter) remain similar (relative risk [RR], 1.70; $P < 0.001$); for the second analysis (CD4+ count of more than 500 cells per cubic millimeter) the risk of death with deferral was slightly attenuated but still statistically significant (RR, 1.53; $P < 0.001$).

In response to Hernán and Robins: we concur that we defined our “early”-therapy group according to whether patients initiated therapy when their CD4+ counts were above each of the two thresholds of interest within a defined window of time. They approach the question slightly differently, defining early therapy only in accordance

with time. However, if we define early initiation only according to time, as they suggest, the results of our first analysis remain similar to what we reported (RR, 1.70; $P=0.006$) and the results of the second analysis are only slightly attenuated (RR, 1.76; $P=0.002$). We were pleased to see that the preliminary results reported with the use of their methods¹ for initiation at a CD4+ count of less than 350 cells per cubic millimeter as compared with initiation at a count of less than 500 cells per cubic millimeter were nearly identical (RR, 1.68; 95% confidence interval, 1.05 to 2.69) to what we reported.

The time frame we defined for initiating antiretroviral therapy best reflects what occurs in clinical practice. We are currently preparing a separate manuscript that will outline the influence of these and other choices on our estimated effect of deferral and note that sensitivity analyses consistently show an increased risk of death with deferral of antiretroviral therapy.

Last, the letters from Gelinck and van der Ende and from Arribas et al. highlight the potential for our results to be confounded. We acknowledge this concern and note that this was the motivation for the simulations in which we found that unmeasured confounding factors would need to have a substantial association with both therapy deferral and mortality in order to have mitigated our results. We are collecting many of the variables noted by these authors and look forward to updating our analyses when these data are available.

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1. Cain LE, Hernan MA. Dynamic marginal structural models to find optimal treatment regimes. *Am J Epidemiol* 2009;169: Suppl:S41. abstract.

Predisposing Factors for Adrenal Insufficiency

TO THE EDITOR: The review of predisposing factors for adrenal insufficiency by Bornstein (May 28 issue)¹ includes a welcome discussion of the limitations of current tests that measure plasma cortisol levels in critically ill patients. However, in the review, stimulation with 1 μg of corticotropin is recommended to identify patients with relative adrenal insufficiency, and I believe the current evidence does not support this.

At least two studies^{2,3} have questioned the reproducibility of corticotropin stimulation testing in critically ill patients. A substantial number of patients appear to have different responses to 250 μg of corticotropin when they are tested on two consecutive days, with results of one test showing adequate adrenal function and results of the other showing inadequate function. Venkatesh et al.⁴ found that hour-to-hour changes in plasma cortisol levels in the same patient are substantial and that spontaneous hourly increases are often greater than the increase of 9 μg per deciliter (250 nmol per liter) that is commonly used to define adequate adrenocortical response.

These issues of reproducibility and signal de-

tection against a noisy background should be resolved before corticotropin stimulation testing can be recommended to identify relative adrenal insufficiency.

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1. Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009;360:2328-39.
2. Bouachour G, Roy PM, Guiraud MP. The repetitive short corticotropin stimulation test in patients with septic shock. *Ann Intern Med* 1995;123:962-3.
3. Loisa P, Uusaro A, Ruokonen E. A single adrenocorticotropic hormone stimulation test does not reveal adrenal insufficiency in septic shock. *Anesth Analg* 2005;101:1792-8.
4. Venkatesh B, Mortimer RH, Couchman B, Hall J. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. *Anaesth Intensive Care* 2005;33:201-9.

TO THE EDITOR: According to a recent consensus conference, adrenal insufficiency in critical illness is best diagnosed by an increase in cortisol (in response to the injection of 250 μg of corticotropin) of less than 9 μg per deciliter or a random total