Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: 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. DOI: 10.1056/NEJMoa0807252.

Supplemental Methods

Censoring:

In a randomized clinical trial, participants would adhere to a protocol to initiate treatment within a specified time window after their CD4+ count reached a particular target (e.g. initiate antiretroviral therapy immediately when the CD4+ count is within the range of interest or defer and initiate antiretroviral therapy if CD4+ count falls below a threshold value). Participants in our observational analysis do not necessarily follow this specified protocol: individuals who delay initiating therapy beyond the target window, or do not initiate at all, would be considered 'outside of trial protocol'. One approach to address these individuals would be to omit them from the analysis as previous studies have done,[23] but this would exclude participants based upon events that occur after the start of follow-up that are prognostic for survival, introducing the potential for selection bias.[26] Alternatively, they can be included in the analysis but censored at the time they deviate from the protocol. Therefore, in the analysis of the first study group, we censored participants who deferred therapy from the time their first CD4+ count was 351-500 cells/mm^3 and either (1) did not transition to a CD4+ count ≤350 cells/mm^3 but initiated antiretroviral therapy outside the target window following their first CD4+ count in the 351-500 cells/mm^3 range; or (2) transitioned to ≤350 cells/mm^3 and further deferred antiretroviral therapy beyond the target window from their first CD4+ count measurement. 'Outside of trial protocol' censoring in the analysis of the second study group used the CD4+ count threshold of ≤500 cells/mm^3. This censoring is not random, thus to attempt to account for dependent censoring, we used inverse probability weighting (IPW) methods developed by Robins[26] and Hernan.[47] We defined a 6 month target window based on the frequency of patient follow-up. Time-updated, person-month datasets were used to construct weights for the 'outside of trial protocol' censoring as well as loss-to-follow-up censoring; weights were stabilized and used in weighted Cox regression analyses. We investigated the sensitivity of the models to influence from individual cohorts by examining estimates calculated with data from each cohort

systematically omitted from the analyses. We also determined whether there were any interactions between therapy deferral and calendar year, cohort, baseline HIV RNA level, history of IDU, HCV infection, and age.

Simulations:

A new variable (*U*) was generated at the individual level such that it was positively associated with therapy deferral (strength measured by a log odds ratio (OR) varying across 8 levels from 1.0 to 4.0) and also positively associated with mortality (strength measured by a log RH varying across 8 levels from 1.0 to 4.0). A cohort- and calendar year-stratified Cox regression model was fit using the same variables as the primary analysis in addition to the new variable *U*. Five replicates for each parameter combination were made and averaged. Contour plots of the 64 simulation results were constructed to examine how the associations with the variable *U* impacted our estimate of the mortality risk of treatment deferral.