

Beneficial impact of antiretroviral therapy on non-AIDS mortality

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The remarkable impact of HAART on HIV-associated mortality has been amply demonstrated [1–5]. Treatment guidelines across the world reflect emergent information regarding benefits of earlier treatment initiation, including reduced AIDS-associated mortality and reduction of the risk of HIV transmission [6,7]. However, non-AIDS conditions as cause of death have become increasingly apparent with the decline of AIDS-related mortality [8,9]. A critical question is whether HAART reduces non-AIDS mortality among HIV-infected persons to levels observed in HIV-uninfected populations.

Wada *et al.* [10], in this issue of *AIDS*, shed significant light on this question in their analysis of AIDS and non-AIDS deaths among early (initiating HAART at CD4⁺ cell count >350 cells/ μ l), intermediate (initiating HAART at CD4⁺ cell count 201–350 cells/ μ l), late HAART initiators (CD4⁺ cell count \leq 200 cells/ μ l) and HIV-uninfected individuals from the Multicenter AIDS Cohort Study (MACS) (men) and Womens Interagency HIV Study (WIHS) (women) cohorts. Their analysis includes proportion, timing and hazard ratios for non-AIDS deaths and AIDS deaths. In terms of AIDS deaths, the study confirms what we already know: late initiators are at significantly higher risk of dying of AIDS-related illness and they die of AIDS at a younger age.

The major contribution of this article lies in the analysis of the proportion of, and hazard ratio for, non-AIDS deaths. Amongst men and women initiating HAART at CD4⁺ cell counts more than 350 cells/ μ l, deaths were more

likely due to non-AIDS causes (than AIDS causes) compared with the late initiator group. Moreover, after controlling for common mortality predictors, the hazard ratios of non-AIDS death were similar for individuals initiating HAART at CD4 cell counts more than 350/ μ l and their uninfected counterparts.

Other recent studies have documented near normal all-cause mortality rates among treated HIV-infected individuals with well controlled viremia and high CD4⁺ cell counts [11,12], relying on standard mortality rates for the general population. What is unique about the current study is the analysis of the effect of treatment on cause-specific mortality (AIDS and non-AIDS deaths) and the availability of a well suited control group from within the cohorts used for the analysis, a key strength provided by the WIHS and MACS cohorts.

Use of the WIHS and MACS cohorts provides other important strengths, offering meaningful data for both men and women. Long-term follow-up and outstanding quality of data, including important information on socioeconomic factors and common predictors for non-AIDS deaths, are critically important and add to the value of this study. In contrast to other studies [11,12], all participants, including injecting drug users, were included in the analysis. The authors strive to minimize the effect of bias inherent in all observational studies, including the lead-time bias. Using age as a time of origin makes particular good use of the advantages provided by the MACS and WIHS cohorts.

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Nonetheless, Wada *et al.* [10] leave readers wondering whether non-AIDS mortality would continue to decline with antiretroviral therapy (ART) initiation at higher CD4⁺ cell counts. Is there a CD4⁺ level above which antiretroviral initiation is not associated with further decreases in non-AIDS mortality? As most of the major guideline committees worldwide now recommend initiating ART at CD4⁺ cell counts of 500 cells/ μ l or less and the Department of Health and Human Services (DHHS) guidelines recommend ART regardless of CD4⁺ cell count, the usefulness of these data would be enhanced by the assessment of the impact of even earlier treatment initiation (>500 cells/ μ l) on non-AIDS mortality. Though the MACS and WIHS cohorts offer lengthy follow-up, the authors analyzed data only through 2009, begging the question whether or not extending analyses to include follow-up data through 2013 would shed further light on the impact of initiating ART at higher CD4⁺ cell counts. As the authors state, antiretroviral treatment and patient management strategies continue to evolve, therefore, inclusion of more recent data from the cohort would be valuable, recognizing that the small numbers of deaths may still limit conclusions.

Wada *et al.* [10] provide further evidence on the critical nature of research addressing non-AIDS complications among HIV-infected persons. Cardiovascular disease was the most common cause of non-AIDS death amongst participants without hepatitis, highlighting the importance of ongoing research addressing inflammation as a factor in cardiovascular disease amongst HIV-infected persons. Strikingly, liver disease accounted for nearly a third of non-AIDS deaths among HIV-infected persons with hepatitis B or C. Given the promise of more effective treatments to cure hepatitis C infection, one hopes that this cause of non-AIDS mortality will diminish in importance.

The question of when to start ART, and how to best answer it remains hotly debated within the global HIV community [13,14]. Difficulties in answering this question through randomized trials include the ongoing improvement and simplification of ARTs, proven impact of HAART to reduce the risk of HIV transmission, and ethical challenges considering evolving consensus among guideline committees to initiate treatment at CD4⁺ cell counts of 500 cells/ μ l, if not above. In HIV, as in other fields, we have come to increasingly appreciate sound, robust, and confirmable analyses based on well conducted cohort studies to complement data from randomized clinical trials. This is true for mortality as well as long-term drug safety assessments. Moreover, confirmation of findings by applying different analytic approaches to different cohorts will contribute to the robustness of the conclusions and facilitate the validation of different statistical methods. Continued public funding of cohorts such as the MACS, WIHS and others will be even more important as we enter the fourth decade of antiretroviral

treatment and seek to optimize treatment strategies to improve individual and public health.

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Conflicts of interest

There are no conflicts of interest.

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