Reply to Young et al

TO THE EDITOR—We thank Young and colleagues for their interest in our paper [1, 2]. We address the issues raised in this response.

The authors state that risk should be modeled as a function of cumulative rather than current exposure. It is entirely plausible for current antiretroviral exposure to affect cardiovascular risk. This has been found in other drug classes, for example, the increased risk of acute myocardial infarction immediately following exposure to celecoxib [3] and the rapid reduction in risk following use of statins [4]. Whether the risk from antiretroviral drugs is from recent or cumulative exposure is an important question. We explored the risk from cumulative exposure as a secondary analysis, and it did not contradict the findings from our primary analysis.

The authors imply we did not use the sensitivity analyses recommended by Cole and Hernan [5] and claim that our marginal structural weights excluded dyslipidemia, lipodystrophy, and previous values of CD4 and viral load. We considered these and other variables, including lipid profiles, kidney function, and blood pressure, among others. Different weighting schemes had little impact on the results, although the stability of the weights varied. Our final weighting scheme included viral load and CD4 count in the previous time interval and exposure to statins for 1 year or longer, among other variables.

The authors claim that an excessive number of adjustment variables made the estimates from our Cox models too precise and inflated and that hierarchical models should have been considered. In secondary analyses to assess sensitivity of model choices, we considered Cox models with and without adjustment for approximately 30 variables and found that point estimates and standard errors were essentially unaffected. The number of terms had little impact on inflating estimates or underestimating standard errors. We agree that tools other than Cox models are potentially useful, but we addressed the authors’ concerns via extensive sensitivity analyses.

The authors suggest that we did not consider alternative multiple imputation models. We made use of the joint modeling approach (as opposed to the fully conditional specification approach) for multiple imputations. We presented findings based on the most inclusive imputation model considered. As demonstrated by Collins et al [6], an imputation model that is more inclusive will result in estimates that are less biased and more efficient under a given missing data mechanism.

We did not report all sensitivity analyses but focused on those that were of greatest interest to the reader because they could affect our findings, such as the discovery that there was a discrepancy between the results of the marginal structural models and the extended Cox model. We described these differences and provided our rationale for relying on the marginal structural models.

Finally, the authors imply that providing code could potentially encourage thoughtless implementation of our methods. We made our code available to provide transparency. As with any study, use of code developed by others requires careful consideration of its methodologic underpinnings.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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