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Lost Opportunities Concerning Loss-to-Follow-Up: A Response to Elul et al.

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To the Editors

My colleagues and I read with great interest the recent publication from Elul et al.,[1] which attempts to 'untangle' the relationship between antiretroviral therapy (ART) use and incident pregnancy among HIV-positive women in East Africa. While we applaud the authors' use of competing risk analysis and marginal structural models, we have concerns about their decision to treat loss-to-follow-up (LTFU) as a competing risk and for not considering the possibility of informative censoring.

A competing risk, like death, prevents a given individual from experiencing the outcome of interest, whereas a censoring event merely prohibits the researchers from observing the outcome. Treating a competing risk as a censoring event will overestimate the outcome incidence; alternatively, treating a censoring event as a competing risk will underestimate it. In this study, LTFU was treated as a competing risk, which is problematic. In clinic-based studies, it is sometimes appropriate to consider loss to care a competing risk, particularly if loss to care precludes the outcome of interest (e.g., treatment initiation) or implies imminent death.[2] However, LTFU does not always equate to loss to care, since individuals LTFU can enroll in care, including prenatal care, outside of the study.[2,3] While Elul et al. treated transfers as censoring events, there was no discussion on the study's ability to observe transfers or whether transfers could be misclassified as LTFU.

The treatment of LTFU as a competing risk could partly explain the low estimated incidence of pregnancy in this study, compared with other work.[4,5] The amount of underestimation is a function of the proportion of women who transferred but were misclassified as LTFU. HIV-positive pregnant women have high rates of LTFU,[3,6–8] and it is reasonable to assume that women recently pregnant or seeking to become pregnant may have similar LTFU patterns. Elul et al. do not discuss the proportion of LTFU in their study (or the deaths and transfers observed), which makes estimating the potential bias difficult. Perhaps most importantly, treating LTFU as a competing risk limits the estimate to the effect of ART use on incident

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pregnancy *while under follow-up*. This is not the same as the effect of ART use on pregnancy (unconditional on remaining under follow-up), although it could be misinterpreted as such.

The authors could have instead treated these women LTFU as informative censoring events. When LTFU is not predicted by any covariates, meaning those who remain are a random sample of those who started, censoring can be considered uninformative, and no bias will be introduced by censoring those LTFU. However, if LTFU is predicted by the outcome or has a common cause with the outcome, i.e. informative censoring, ignoring it will introduce bias.[9] Because it is likely that LTFU is associated with pregnancy, it is necessary to assume that informative censoring has occurred. Moreover, if LTFU was differential by ART use, the effect estimate could be biased in ways that are difficult to predict.

The best approach to account for this informative censoring depends upon the expected causal relationship between LTFU and the outcome. If the outcome (unmeasured because of LTFU) directly affects LTFU or LTFU affects the occurrence of the outcome, there are currently no available methods to handle the informative censoring, although sensitivity analyses can be used to estimate its effects. Alternatively, if LTFU has measured common causes with the outcome, but does not affect the outcome itself, then inverse-probability-of-censoring weights can be used to handle the informative censoring. Using censor weights creates a pseudo-population where censoring is uninformative, conditional on the covariates included in the weight models, and removes the ‘while under follow-up’ condition on the effect estimate. Like weights for confounding, they can easily be incorporated into marginal structural models. Methods to create and apply censor weights have been recently described.[9,10]

Finally, we are concerned by the authors’ use of a Cox proportional hazards model for the effect measure modification analyses. As the authors state, a multivariable Cox model, while comparable to previous research, provides biased estimates due to inappropriate adjustment of covariates, like CD4 count, which are both time-varying and affected by prior exposure.[11] It is unclear why the authors did not extend their use of marginal structural models to the effect measure modification analysis, as these models can be adapted to examine modification by baseline variables as well as interaction.[12,13]

Overall, this article provides an important step forward in the use of causal inference methodology in studies related to HIV and pregnancy by highlighting the attractive properties of marginal structural models and competing-risk analysis. However, the issues discussed above indicate that more discussion on how to appropriately apply these methods, what it means to consider someone LTFU, and the impact of LTFU are still needed.

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