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Rejoinder to “Lost Opportunities Concerning Loss-to-Follow-Up: A Response to Elul et al.” by Strassle and colleagues

Constantin T. Yiannoutsos, PhD,

Indiana University Fairbanks School of Public Health, Department of Biostatistics, Indianapolis, USA

Kara K. Wools-Kaloustian, MD,

Indiana University School of Medicine, Division of Infectious Diseases, Indianapolis, USA

Beverly S. Musick, MS, and

Indiana University School of Medicine, Department of Biostatistics, Indianapolis, USA

Batya Elul, PhD, MSc

Department of Epidemiology, Mailman School of Public Health, Columbia University; ICAP at Columbia University, New York, New York, USA

In response to the letter by Strassle and colleagues, we would like to provide a rejoinder regarding some of the salient points raised by these authors. To do so, it would be useful to address each of these issues separately in order to clarify some of the confusion that may exist about the statistical analyses in our paper [1].

The first issue raised by Strassle et al concerned the treatment of loss to program in our analysis. Loss to program (also referred to as loss to follow-up or patient dropout), particularly in the low to middle-income settings where we work, prevents complete observation of a number of patient outcomes. Of most relevance to our paper, loss to program limited observation of incident pregnancies but also other relevant factors such as re-engagement in HIV care at programs outside the initial clinical site and mortality following dropout. For this reason, we considered loss to program as a competing risk rather than an event censoring the time until the experience of an incident pregnancy, our endpoint of interest. It is critical here to recognize that this choice has *no bearing on the ultimate numerical estimates* of the impact of antiretroviral therapy (ART) on the likelihood (hazard) of incident pregnancy, but rather affects solely the *interpretation* of the results. The reason is that, operationally, loss to program abbreviated the follow-up time in all analyses presented and thus resulted in censoring along with all other events limiting complete follow-up such as death and known transfers, in addition to administrative censoring (end of observation due to database closure) resulting in the end of follow-up. When loss to program is modeled as a

Corresponding author: Batya Elul, Mailman School of Public Health, Columbia University, 722 West 168th Street, 528, New York, NY 10032, be2124@columbia.edu, Tel: 646 303 2441.

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competing event, ART is considered a risk factor for the cause-specific hazard of experiencing an incident pregnancy versus the cause-specific hazards of experiencing other events such as death, loss to program or transfer to another care and treatment facility. So, absent some correction on the current estimates, resulting from additional data obtained from some or all of the dropouts [2, 3], or sensitivity analyses based on historical or otherwise external data, our estimates of the effect of ART on incidence pregnancy do not change whether loss to program is viewed as a competing risk or a censoring event.

Strassle and colleagues additionally noted that loss to program may have downwardly biased estimates of the impact of ART on incident pregnancy. While we concur with this assessment, we do not agree that attenuation of the estimates is necessarily the result of informative censoring induced by loss to program. As is well known [4], even non-informative censoring can attenuate associations between a risk factor and the outcome of interest. Informative censoring on the other hand, may result in underestimation or overestimation of the true effect [4, 5] as the authors correctly state. However, their proposed remedy, inverse probability of censoring weighting (IPCW) methods [6], is unlikely to fully address these biases because data in patients lost to program in this setting are, most likely, not missing at random (MAR) [7], a key assumption in IPCW methods. In the presence of data missing not at random, the effect of ART could have been underestimated or overestimated in ways that are not obvious. For example, it could have been underestimated given the propensity of pregnant women to drop out of care at higher rates compared to the general patient population (see for example the references cited by Strassle and colleagues [8–11]). As these women are more likely to experience an incident (repeat) pregnancy, as per our analysis, dropping out of care may reduce the ranks of patients on ART who are more likely to experience an incident pregnancy (since their probability of accessing ART after leaving an HIV care and treatment program is likely much lower). On the other hand, the effect of ART on pregnancy, which is based on our analysis of patients under observation, may also have been overestimated, if a significant portion of loss to program were due to unreported death, particularly among the sickest of patients who may also be less likely to get pregnant [11] (resulting in the attrition, among patients receiving ART, of those who might be less likely to experience an incident pregnancy while on treatment). Unfortunately, the proportion of patients who belong to each of these groups, as well as HIV-care seeking behaviors after leaving the current program can only partially be estimated based on data obtained while these patients were in care (the very essence of data missing not at random).

Instead of speculating about these disparate sources of potential bias, we opted instead to account for biases which are addressable based on the data available to us. The largest and most obvious of these was bias arising from “time-dependent confounding” of the role of ART on pregnancy [12]. Such confounding was produced by factors associated both with the probability of an incident pregnancy and with the likelihood of ART initiation. These included CD4 count, weight, and World Health Organization (WHO) stage, contextual factors of care plus, most notably, previous pregnancies. In particular, measures of disease severity are associated with the likelihood of initiating therapy and, once therapy commences, are affected by patient response to ART. To minimize the effect of such biases, we used inverse probability weighting (IPW). The corrected estimates transformed an apparently detrimental impact of ART on pregnancy to a marginally beneficial one, albeit

much lower than what has previously been reported. In the discussion of our paper, we provided a number of possible explanations for this departure from the previous literature. This included the fact that most prior studies did not fully account for the role of previous pregnancies in their cohort selection and, in one case, explicitly recruited women who were either pregnant or had recently become pregnant[13]. Given policies to prevent mother-to-child transmission of HIV, women who experience prior pregnancies constitute a large subgroup of women starting therapy with less advanced disease (the subgroup of women most likely to experience a subsequent pregnancy).

In conclusion, while, we cannot discount the possibility that biases arising from loss to program may have resulted in an underestimation of the impact of ART on incident pregnancy, absent additional information on the dynamics between loss to program, pregnancy and HIV disease, our analyses exhaust what can be gleaned from observational data collected as part of routine clinical care in this setting.

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