Reviewer’s report

Title: Pregnancy loss and perinatal mortality among HIV-infected women: role of infant HIV status

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Reviewer: Benjamin Chi

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MAJOR COMMENTS

In the abstract, discussion, and conclusion, the authors appear to attribute causality between HIV infection and later outcomes, with use terms such as “contribute” and “attribute.” In my reading of the paper, there doesn’t seem to be a basis for this, since only associations are described. Please comment.

Classification of pregnancy loss is based on gestational age; yet, the authors do not describe how gestational age was determined. Was last menstrual period validated by clinical exam and/or ultrasound? Were changes made because of inconsistencies between the methods?

For their estimates of stillbirth and miscarriage rates, the authors use conventions that compare these outcomes to live births. My understanding is that these ratios are based on an assumption that the sample population begins at a common timepoint. For example, if all participants started at 24 weeks gestation, then the stillbirth rate per 100 (or 1,000) live births seems appropriate. In the situation where enrollment may occur over a wide range of gestational ages, however, there will be inherent bias. Those who survived to an older gestational age (and enrollment) may not be representative of the larger population. This problem of selection bias is most pronounced in the miscarriage estimates, since in most African settings antenatal care does not begin until well into the second trimester. At the very least, this deserves thorough commentary in the discussion, since it likely resulted in underestimates of miscarriage – and of possibly stillbirth as well. It might also be possible to correct for this bias analytically.

How was HIV infection status handled if infants became LTFU prior to 42 days? In the sensitivity analysis, the authors seem to suggest that these infants may have been classified as having unknown HIV status, but it’s not explicitly stated anywhere. Please clarify.

The authors describe both LBW and preterm births (PTB) as study outcomes. There is obviously overlap between these two measures and, in fact, LBW has been used as a surrogate marker for PTB in other analyses. In my opinion, both outcomes are not needed. The authors should consider removing the PTB analysis, particularly given the suspected inaccuracies around gestational age for participants in the study.
MINOR ESSENTIAL REVISIONS

Title: The second part of the title (role of infant HIV status) does not apply to the pregnancy loss part of the analysis.

Abstract introduction: The association between HIV infection and pregnancy loss – in particular stillbirth – has not been consistent in the medical literature. The authors should consider modifying their opening sentence, perhaps saying that HIV-infected women MAY have higher rates of pregnancy loss.

Abstract results: The OR to describe the association between stillbirth and “being symptomatic” seems to be missing.

Methods: Gestational age at time of enrollment is important in this analysis. If there were any eligibility criteria dealing with gestational age, these should be included in the Methods. Breakdown of enrollment GA should be included in the results.

Results: Please include 95% confidence intervals around estimates for miscarriage and stillbirth (lines 180-182) and neonatal / early infant mortality (lines 248-250)

Results: I found the third paragraph of “Risk factors for neonatal and early mortality” difficult to follow. I wonder if the multivariable analysis might be better presented in a table rather than in text. The final sentence of the same section needs to be either removed or revised with greater detail.

Results: At numerous points, the authors list all the descriptors together and then all the corresponding figures together, followed by the word “respectively.” This sentence construct is difficult to follow, particularly when many items are listed. Lines 248-250 include an extreme example of this and needs to be corrected for readability. However, I would urge similar edits be made throughout the paper.

Tables: With the current PTB analysis, the authors use a threshold of 34 weeks for classification. They provide a rationale in the paper, but I would avoid describing those > 34 weeks as “term.” A term pregnancy has a very clear definition and it is based on a 37-week threshold. The tables need to be revised accordingly.

Tables 1-4: Are these adjusted or unadjusted analyses? Please include that detail in the table title or as a footnote.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests