Author's response to reviews

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

Authors:

Hae-Young Kim (hk2553@columbia.edu)
Prisca Kasonde (pkasonde@fhi.org)
Mwiya Mwiya (mwiya2002@yahoo.com)
Donald M Thea (dthea@bu.edu)
Chipepo Kankasa (ckankasa@zamnet.zm)
Moses Sinkala (mosessinkala81@msn.com)
Grace Aldrovandi (galdrovandi@chla.usc.edu)
Louise Kuhn (lk24@columbia.edu)

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Author's response to reviews: see over
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Dear Editors

We thank the editors and reviewers for their interest in our manuscript and the careful review of our work. Below we describe the changes we have made in response to the comments and attach a version of the manuscript with all the changes marked in track changes. We believe the manuscript is greatly strengthened.

Reviewer: Benjamin Chi

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.

Response: We agree that there are limitations of epidemiologic studies to ascribe causality. However, in this analysis, we are particularly interested in factors other than infant HIV infection as potentially explaining the excess mortality observed in infants born to HIV-infected mothers. That HIV infection per se increases mortality is well-known and has a clear biological basis. We use the terms “contribute” and “attribute” to help clarify our focus on the other characteristics being investigated.

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 changed made because of inconsistencies between the methods?

Response: Gestational weeks at enrollment was estimated from reported last menstrual period and fundal height measured by mid-wives. Gestational age measured by the two methods were closely correlated (r=0.62). When there were inconsistencies between reported last menstrual period and corresponding fundal height, last menstrual period was used to estimate gestational age.

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.
Response: We appreciate the reviewer’s comment. We agree that there could be selection bias resulting in underestimation of miscarriage or stillbirth. Many of women in our study were enrolled into the study during the second trimester (median = 26 weeks; IQR 20-31). We added comments on this selection bias in discussion section.

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.

Response: As indicated in sensitivity analysis, the 50 infants with unknown HIV status either died or lost to follow up before 70 days (<42 days). These infants do not have any HIV test results and were excluded from other analyses. Another 69 infants were lost to follow up but confirmed HIV-negative prior to 42 days; these infants were included as NI infants. We have edited the methods and results and hope that this clarifies the classifications.

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.

Response: We agree with the reviewer that the estimates of gestational age can be inaccurate in a study such as ours. Birth weight, which is so much easier to measure, is not prone to this measurement error problem. However, while there is a great deal of overlap between LBW and PTB, conceptually they are quite distinct and have quite different risk factors. LBW is a hybrid outcome – a result of both being born too early and being born too small. PTB, on the other hand, simply reflect being born too early. We would prefer to retain both outcomes given the distinct biological processes they reflect.

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.

Response: This has been corrected.

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.

Response: This has been corrected.

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

Response: This has been corrected.

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.

Response: As suggested, breakdown of enrollment GA was included in the results. No specific GA criteria were a part of the eligibility criteria.

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

Response: This has been done.

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.

Response: As suggested, we rewrote and simplified this paragraph by adding the results into Model 1 in Table 5.

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.

Response: As suggested, we broke down into smaller sentences in lines 248-250 and 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.

Response: Due to apparent systematically underestimating gestational age by about 2-3 weeks, it was necessary to make this unusual cut-point. We have now edited the Tables. We have provided the rationale for the cutpoint in the methods.

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

Response: These are unadjusted analyses. This has been corrected.
Reviewer: Vivian Black

Reviewer's report:

- Discretionary Revisions
In the conclusion, 5th paragraph (line319). Reference is made to WHO guidelines. Which guidelines are these? 2010?

Response: Yes. The reference was added in the paper.