Author's response to reviews

Title: The effect of mode of delivery on HIV-1 disease progression and mortality in a Kenyan cohort

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Author's response to reviews: see over
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RE: Revised Manuscript for BMC Pregnancy and Childbirth; MS 2023872777110212

Dear BMC Pregnancy and Childbirth Editorial team:

Please accept our revision and resubmission of the original research paper: The effect of mode of delivery on HIV-1 disease progression and mortality in a Kenyan cohort.

We appreciate the reviewers’ questions and comments and are happy to address the issues raised.

It was requested that we make the following revisions:

Reviewer 1:

#1 While the authors claim unscheduled CS was an independent risk factor for mortality postpartum, they do not provide any information about the reason for the unscheduled CS; where those uterine rupture cases for example?

Response: This is a clinically relevant point. We have now included all available data for cesarean section indications. Not surprisingly, there are more data available for the non-scheduled cesarean section (NSCS) group given that the indication for CS was recorded as a labor complication. This data is now included in Table 3 and as part of the Results section. The majority of NSCS indications were for obstructed labor (47%). We unfortunately have incomplete data for both groups and particularly for the scheduled cesarean section (SCS) group. We presume some of these were performed for prevention of mother-to-child HIV-1 transmission (PMTCT) but cannot state this conclusively given that this data was not routinely collected.

#2 All information on the postpartum mortality cases should be available for readers so they can evaluate the reason for the mode delivery, the CD4 count status and the reason and timing of the mortality (months after delivery, year of death).

Response: We have included the information about the 13 first year postpartum mortality cases including the cause of death, mode of delivery, indication for mode of delivery, timing of death and last known CD4^+ count. This is important information for understanding the mortality data and we have presented this in Table 4. We have also included this information in the last paragraph of the Results section.

Introduction

#3 The authors describe the rationale for this study: maternal mortality is higher in SSA and treatment guidelines difficult to access. Readers may be very interested in the maternal mortality rate in Nairobi for HIV positive pregnant women outside the study and what is was for HIV negative women with a CS.

Response: We agree that readers may be interested in the maternal mortality rate in Nairobi for HIV positive women outside of the study and for HIV negative women with a cesarean delivery. Unfortunately that is not data specifically collected by the Kenya Demographic Health Survey (KDHS) and is otherwise not available to us. We have however, included the estimated maternal mortality ratio from both Kenyatta National Hospital, where the study took place, and for Kenya as a whole at the time of the study. The average maternal mortality
rate (MMR) at Kenyatta National Hospital at the time of the study was approximately 300 per 100,000 live births similar to the countrywide rate of 488 per 100,000 live births in 2008. The most common causes of maternal deaths in Kenya continue to be maternal hemorrhage and infection, with HIV-1 being a significant indirect contributor.

#4 Readers may also be interested in the treatment guidelines that were available at the moment of the study and the authors may decide to provide this information.

Response: We agree this is an important point given the potential influence of treatment on outcomes. At the time of the study guidelines were short-course zidovudine or nevirapine for prevention of MTCT. We include more substantial information about the treatment guidelines in the Methods section of the paper. (Please see response to #6)

Methods

#5 Was the larger study published? Please provide a reference.

Response: Yes the larger study was published. We provide a reference for the larger prospective cohort study (John-Stewart et al, 2009) in the Methods section.

#6 Did all women receive the short course zidovudine?

Response: Yes, all women received a short-course of zidovudine prescribed according to the Thai regimen, which was standard of care at the time. We add a clearer statement about this in the Methods section and a reference to the article reporting the efficacy of short-course zidovudine for PMTCT (Shaffer N et al, 1999). However, women did receive differing numbers of zidovudine doses based on the length of labor.

#7 Was the ART treatment distributed evenly among the 3 groups? This became available only the last few years when relatively more SCS happened.

Response: Only 1 woman in the analysis was referred for ART treatment during the first year postpartum when it became more widely available. This participant was in the SCS group. The remaining 11 participants were referred for ART during the second year postpartum, which is outside of the scope of this analysis.

#8 The indications for SCS and NSCS should be provided in great detail in such a cohort study.

Response: We have included available data on the indications for SCS and NSCS. Please see our response to #1.

#9 Should ARV use be included in the models as well? or other infections malaria, diarrhoea?

Response: Very few women received ARVs and therefore this was not included in our models. We did not specifically examine the role of other infections such as malaria and diarrhea in the multivariate models because they were evenly distributed between the VD and NSCS groups.

Results

#10 What was the original size of the study cohort – when there was delivery information available for 501 – could there have been any selection bias?

Response: The original size of the study cohort was 535 women. We were missing delivery data for only 34 women (6% of the entire cohort). We did not include these participants in any portion of the analysis. The small number of missing is unlikely to create bias.

#11 Why was there a dramatic increase in SCS over the years?

Response: The data from The International Perinatal HIV Group and The European Mode of Delivery Collaboration demonstrating a lower risk of mother to child transmission of HIV with cesarean section before labor and ruptured membranes was published in 1999. Practice protocol changes started in Kenya in 2000 but
were not standard of care at the time of this study. These practice changes are likely reflected in the increase in SCS but unfortunately we are not able to conclusively state the indications for SCS because the data was not well recorded.

**#12 Longer labors – how did the authors defined start of labor? And how was this documented in the records**

**Response:** The reviewer points out an important and very challenging factor when conducting studies with variables of interest including duration of labor. In this study the onset of labor, and therefore labor duration, was determined from a review of the medical records, which relied on physical exam and patient self-report. However, in this case we were not able to follow a rigid definition for the onset of labor.

**#13 Number of available postpartum CD4 counts/ RNA were distributed relatively even among the groups?**

**Response:** The percentage of available postpartum CD4+ counts and HIV-1 RNA data was evenly distributed among the three groups. We add this detail to the Results section under postpartum immunologic progression and virologic progression.

**#14 All clinical details of the 13 dead women should be provided – diagnosis, timing, reason for CS etc.**

**Response:** We now include the information about the 13 first year postpartum mortality cases including the cause of death, mode of delivery, indication for mode of delivery, timing of death and last known CD4+ count. We agree with the reviewer that this is important information for understanding the mortality data and we now present this in Table 4. We also include this information in the last paragraph of the Results section.

**#15 Did the authors consider to include other confounding factors: parity, other infections (malaria?), socio economic status?**

**Response:** We did consider other confounding factors to explain the postpartum mortality. Although we agree that all of the mentioned factors (parity, SES and other infections) likely played a role in the individual deaths, these factors did not differ significantly between the VD and NSCS groups. Malaria is not prevalent in Nairobi and very few women had other infections. The women who died did have infections related to HIV as now presented in the mortality data.

**Discussion**

**How do the authors think the findings may influence labor or postpartum management?**

**Response:** The findings of this study build upon previous studies demonstrating the highest risk of complications and mortality occurs in women who deliver by NSCS. In our cohort, neither duration of labor nor duration of rupture of membranes appeared to explain the higher risk of mortality in women in the NSCS group. Other studies have examined the effect of mode of delivery and HIV on postpartum morbidity and found the highest risk of morbidity in HIV+ women who undergo NSCS. We found higher mortality in the NSCS group suggesting that this group may require closer postpartum follow-up in the first year.

**Table 2**

**In which years the deaths happened?**

**Response:** Please see the new Table 4

**Figure 3**

**Could the authors provide the number of patients available in a table below the graph**

**Response:** Please see the new Table 4

**Reviewer #2**

**#1 The main issue with the article is that it was not powered to determine this association, and the sample size is skewed towards those who delivered vaginally**
Response: While we appreciate the reviewer’s observation that the number of women who delivered by NSCS was smaller than the number of women who delivered by VD, our study was powered to detect the association between mode of delivery and first year postpartum mortality as evidenced by the confidence interval. The 95% CI supports the finding that women who underwent NSCS were 3 times more likely to die in the first year postpartum than women who underwent a VD (95% CI 1.11, 10.35, P = 0.03).

#2 There is not attempt by the authors to explain why women with NSCS had higher mortality rates despite the fact that all groups had similar traditional markers of HIV progression in all groups postpartum

Response: As the reviewer suggests, we are not able to fully explain why the women in the NSCS had higher mortality rates. Detailed comparisons of CD4+ and viral load did not suggest differences between the groups, however it is possible for other cofactors to affect HIV-mortality without discernable impact on HIV progression markers if there is limited power, differential ascertainment or insufficient data points. Immune activation has been shown to be an independent marker of HIV-1 disease progression. Major abdominal surgery following labor likely increases immune activation beyond a vaginal delivery or planned cesarean section. Although we cannot support this hypothesis from this data, previous studies have suggested that trauma and surgery stimulate immune activation. In future studies we plan to explore immune activation associate with surgical delivery.

#3 it is however stated that women with NSCS had lower CD counts and higher mean HIV copies, and tended to deliver by c/section as the years of study went by, possibly suggesting that clinicians could have opted to perform a cesar to prevent MTCT, - it is not noted what the stage of the HIV disease was at the time of deliver - could they already have been AIDS - a suggestion of this is made under “discussion”

Response: The reviewer is correct we did find that women in the NSCS had lower baseline or antepartum CD4+ counts and higher HIV-1 RNA levels. However this group was allowed to labor and only underwent a CS delivery after the onset of labor. In most cases these women underwent a CS after a diagnosis of obstructed labor or fetal distress and not for PMTCT. At the time of the delivery there was no significant difference in HIV-1 RNA levels between the groups.

#4 women with NSCS had relatively longer labors, and ended up with NSCS, it would have been interesting to find out the immediate postpartum condition, eg in the 1st 72hours or even 2weeks

Response: We agree with this reviewers comment. Unfortunately data is not available to comprehensively assess the immediate postpartum morbidity.

#5 did the stress of labour and NSCS have a detrimental effect on the condition of the women

Response: We agree with reviewer that the stress of the NSCS recovery combined with untreated HIV likely had an effect on the health of the women in this group.

#6 how soon after the delivery by NSCS did the patient manifest AIDS related diseases

Response: Deaths from AIDS-related illnesses occurred as early as 1 month postpartum in the vaginal delivery group and at 4 months in the NSCS group.

Editors Comments:
Comments to be passed to the authors: Please pay particular attention to the important comments made by reviewer 1. I very much agree with him that we should have knowledge about indications for CS and causes of death in this particular population. In general, mortality after CS is and will be higher compared to VD, this goes not only for the HIV-positive.

Response: We appreciate the comments and have addressed the important issue of indications for CS in Table 3 as well as the body of the paper. We also agree that mortality after CS is always higher and especially so for HIV-positive women.
In this study we found that among HIV-1 infected women in Kenya, non-scheduled cesarean section (NSCS) was associated with a higher risk of mortality in the first year postpartum than vaginal delivery or scheduled cesarean section (SCS). These findings differ from other studies performed in United States and European cohorts and add important considerations to the literature regarding HIV positive women and effects of cesarean section after labor.

We appreciate your comments and look forward to a positive response from your reviewers.

Sincerely,

[Signature]

Jennifer Unger, MD, MPH