Author’s response to reviews

Title: Factors associated with HIV infection among children born to mothers on
the Prevention of Mother to Child Transmission programme at Chitungwiza
Hospital, Zimbabwe, 2008

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Author’s response to reviews: see over
Dear Team

RE: RESPONSES TO REVIEWERS’ COMMENTS

TITLE: Factors associated with HIV infection among children born to mothers on the Prevention of Mother to Child Transmission Programme at Chitungwiza Hospital, Zimbabwe, 2008

Kindly receive the attached the revised manuscript for consideration for publication in your widely read journal.

We have provided a point-by-point response to the reviewers’ comments as outlined below:

Reviewer's report [1]
Title: Factors associated with HIV infection among children born to mothers’ on the Prevention of Mother to Child Transmission programme at Chitungwiza Hospital, Zimbabwe, 2008
Version: 2 Date: 10 June 2013
Reviewer: MaricianaHatienoOnono

Reviewer's report:

A. Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract:
There are a few typographical errors that need to be corrected

*We have revised the abstract to remove typographical errors*
Methods section: need to include a sentence on the analytical methods used

We have revised the methods to include analyses done

Conclusion section: last sentence beginning, “so we recommend that – is incomplete and unclear

We have revised the conclusion to ensure clarity

B. Major Compulsory Revisions

Background
II. Paragraph 1: Need to cite the most recent data: According to UNAIDS, about 330,000 children were newly infected with HIV in 2011. Suggested link - http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/jc2296_unaids_

We have revised the paragraph citing most recent data

III. Paragraph 2: Use the statistics from the UNAIDS report of 2012 or the WHO progress report of 2011

We have revised the paragraph citing most recent data

IV. Paragraph 3 on the goals of the Zimbabwean PMTCT program. I will suggest tightening up this section a little bit and include the national goals of the Zimbabwean PMTCT program to attain the MDGs e.g. is it to reduce MTCT by 90% by 2015. While it is true that the Zimbabwe is one of the countries worst affected by the HIV/AIDS pandemic, according the UNAIDS report:”together we can end AIDS”, Zimbabwe is actually on track to meet the ambitious 2015 target to eliminate new pediatric HIV infections.

We have revised the whole paragraph to include national goals and acknowledge that the country is on track to eliminate new pediatric HIV infections

V. Paragraph 4:
Some very good points made. Also talk briefly about Africa and how breastfeeding/mixed feeding is the norm and the challenges of formula feeding in resource limited settings.

We have discussed breastfeeding as a norm and the attendant challenges in limited resource settings

VI. Paragraph 5:
Numerous citations are missing. Need to link with the importance of breastfeeding within and without a high HIV prevalence setting

We have reviewed more literature and included new citations in the report.
VII. Paragraph 6
Consider merging this with paragraph 3 on the goals of the Zimbabwe PMTCT program and compare, contrast and link with global goals

This paragraph has been merged with the suggested paragraph.

VIII. Paragraph 7
You state that 25% of the HIV exposed infants (HEIs) tested positive at 18 months. Do you have figures for an earlier time point say 6 months? What is the breastfeeding prevalence of Zimbabwe as per the Demographic health survey?
Question – it’s not clear whether the phrase, “already on the PMTCT programme) means that mothers are on ART for PMTCT or ART for their own health or both.
Are you implementing Option A or Option B for PMTCT?

We have no data on HEIs testing positive from an earlier period
We have included the prevalence of breastfeeding from the demographic health survey. We have also defined the phrase ‘on the PMTCT programme’. The country is currently implementing Option A but at the time of the study, we were using single dose nevirapine only.

Methods
I like the case control design.

I. Paragraph 1
What is the rationale for not matching? Statistically speaking if we assumed median duration of breastfeeding among women living with HIV is 12 months and transmission is 1.57 per month among those with CD4 counts less than 350 and 0.51 per month among women with CD4 counts more than 350, It may not be proper to compare a child who is 2 months to that one who is say 9 months. They have had longer exposure. – Please add a sentence justifying the reason for not matching at least on age of child.

We did not do the strict sense match cases and controls as that would entail us doing a matched analysis and not be able to analyze on the matching variable. What we therefore did was frequency match the cases and controls on age to take care of the possible differences in exposure that would arise by difference in age and still be able to analyze the age variable.

II. As stated above – please include a brief description of the PMTCT program. At the time the protocol was being implemented, what PMTCT guideline was being implemented for example: did the women all receive HAART, or were they on short course ART and from what gestation age?

We have included a brief description of the PMTCT program at the time the protocol was implemented.

III. Also include what was your inclusion and exclusion criterion mentioned at the end of the paragraph

We have added a section on inclusion and exclusion criteria.
IV. Paragraph 2
Please include details on
What was the study period?
How were potential mothers (participants) identified and approached?
Was mother’s permission sort to check the status of the infant?

*We have revised the paragraph to include the study period, how participants were identified and approached and the permissions obtained.*

V. Paragraph 3:
Subtitle “permission to carry out the study and ethical considerations” – can be rephrased to simply say “ethical considerations”

*We have rephrased as suggested by reviewers*

VI. Paragraph 4
Subsection on limitations is misplaced and should move to after the discussion section

*We have moved the section on limitations to come after the discussion.*

**Results**
Paragraph 2: Maternal factors
VII. Include the median and range CD4 for the controls

*We have included the median and inter-quartile range for the controls*

VIII. Data on STIs – state it as n (%)  

*We have stated the data on STIs as n (%)*

IX. Clarify if all vaginal deliveries were by skilled birth attendants or home deliveries. This will also affect your MTCT rate

*The deliveries were conducted by skilled birth attendants.*

Paragraph 3: Nevirapine Adherence
X. Sentence 1: Clarify that this is Nevirapine for mother as in single dose Nevirapine.

*Nevirapine for the mother was given as a single dose. We have included this in the methods.*

XI. Nevirapine for babies – how long was the Nevirapine given (short course or extended Nevirapine (I think that this can be catered for, if in the methods section you expound a little bit on the PMTCT protocol being used in Zimbabwe.)

*We have included in the methods that nevirapine was given as a single dose.*
XII. Paragraph 5: State the duration of time that the cases and controls had practiced exclusive breastfeeding

*We have stated the duration of time which the cases and controls said to have practices exclusive breastfeeding.*

Discussion

Paragraph 1

XIII. Phrase “mother infant transmission”: the standard term is mother to child transmission (MTCT)

*We have revised the phrase so that it conforms to the standard terminology as suggested by reviewer.*

XIV. Please verify the citation for this paragraph on factors affecting MTCT. There are multiple literature on this

*We have verified the citation on factors affecting MTCT*

Paragraph 3

XV. The statement – most women had their children tested between six weeks to three months – this is new information most suitable in the methods or results section.

*We have revised to include this in the results section.*

XVI. Please merge paragraph 4 with paragraph 3 since it is strengthening your argument. Also add more literature on this very important point.

*We have merged paragraphs 3 and 4 and added more literature on this point.*

XVII. Some suggested literature
We have reviewed the suggested literature and used some of it as our references.

Paragraph 5
XVIII. Sentence beginning, “the most common cause of the hospitalization was pneumonia, ARI and diarrhoea”…”ARI and diarrhoea were not mentioned in the results section. New results should generally not be introduced in the discussion section.

We have revised the sentence to include the other two common causes of admission.

Paragraph 6
XIX. This is an important paragraph. However, you need to contextualize it; discuss implications (pros/cons) in low resource settings

We have tried to contextualize and discuss the implications of this observation in low resource settings.

XX. Same as comment above, new data (about the cesarean sections) must first be presented in the results before being discussed. Also clarify if the C-sections being referred to were elective or emergent.

We have included the data in Table 3 which was missing in the report first submitted

Paragraph 7, 8 & 9
XXI. Merge this with paragraph 6 and make more concise. Always contextualize it. Some of the sentences are redundant e.g. paragraph 8 – the sentence beginning, “the mode of delivery…” and the sentence “caesarean section has been ……”

We have merged these paragraphs and tried to make them more concise.

XXII. Need to include a paragraph on the limitations and possible strengths of your study methodology before the conclusion

We have included a paragraph on limitations of the study methodology as suggested

CONCLUSIONS:
XXIII. There are numerous research showing benefits of exclusive breastfeeding for a minimum of 6 months and not 4 and even beyond particularly in resource limited settings such as Zimbabwe. Early cessation of breastfeeding is associated with increased morbidity and mortality among infants even regardless of HIV exposure. Coovadia and colleagues in South Africa documented a higher HIV-free survival among the exclusively breastfed than among the replacement-fed infants and that mortality at three months was almost doubled in the group who received infant formula compared with the exclusively breastfed infants

We have revised the conclusion to include the concerns of the reviewer.

*We have referenced the 2010 Guidelines on HIV and infant feeding as recommended*
Reviewer's report [2]
Title: Factors associated with HIV infection among children born to mothers on the Prevention of Mother to Child Transmission programme at Chitungwiza Hospital, Zimbabwe, 2008
Version: 2 Date: 21 May 2013
Reviewer: KwasiTorpey
Reviewer's report:
The paper discusses factors associated with HIV infection among children born to mothers on PMTCT program in Chitungwiza Hospital in Zimbabwe, 2008. Generally the information in the paper seems out of date as it discusses the use of single doses Nevirapine as intervention. There are several areas within the paper that must be revised to make it publishable.

Major compulsory revisions
1. The 2nd paragraph of the Background needs to be properly referenced. i.e. the Joint United Nations Program on HIV/AIDS (UNAIDS) reports.............. In addition, subsequent sentences e.g. It is believed that about two thirds...........should be referenced

We have revised the paragraph and included references as suggested.

2. The background will be stronger if the authors present an overview of HIV in Zimbabwe briefly discussing prevalence, burden of disease and the national response. Most of the information provided on PMTCT are very generic and not specific to Zimbabwe

We have provided an overview of Zimbabwe discussing the prevalence, burden of disease and national response

3. Page 5, Paragraph 2: Information on Chitungwiza Hospital and the services provided will be better under Study context under the methods section.

We have provided information on Chitungwiza Hospital and the services provided under the study context and setting in the methods section.

Methods
4. What do the authors mean when they say someone is on a PMTCT program? Is it receiving maternal or infant prophylaxis or both? Or is it receiving testing and counseling and getting results?

We have defined what we meant by ‘on the PMTCT programme and clarified what it was in the relevant paragraph.

5. What is the scientific basis for the determination of sample size of 120?

We have stated the assumptions we took into account in arriving at the sample size in the methods section.
6. Limitation of study can be mentioned after discussion segment

*We have moved the limitations to after the discussion as advised.*

**Results**

7. Median age for the children was 17 (Q1 =12 Q3=27) for cases and 24 for controls. What is the unit? Months or years?

*The unit for children is months. We have corrected that in the text.*

8. Maternal factors: Median CD4 for cases 180 what about controls?

*We have inserted the median CD4 count for the controls*

9. NVP adherence: How high is 'high'? What about the adherence in both mother and infant? Risk factors: No. Table 3 in the manuscript.

*We have revised the statement to include some quantification of being ‘high’. The NVP adherence in mother is the one in Table 3. Mothers were given the tablet to take home when they were reaching their expected date of delivery so that they swallow it at onset of or during labour.*

10. Multivariate analysis: All the variables that were significant at 0.25 level was included ...... If 0.25 is used as the level of significance, then the likelihood of events occurring by chance is very high

*We used a CDC document “Sexually transmitted infections in Kuwadzana, Zimbabwe” which recommends that cut off point. The reason is that we also did not want to miss any factor which may not have been significant in the bivariate analysis that would be significant on multivariate analysis*

11. Multivariate analysis: Table 4 shows 4 variables......... There is no table 4 in this paper

*We have inserted table 4 which was missing*

12. There two major factors driving HIV infection in infants and these are ARV prophylaxis and breastfeeding. This paper discusses breastfeeding but is almost silent on the prophylaxis. It will be helpful if more information is provided on the maternal and infant prophylaxis in a tabular form

*We have made an effort to review and include in our discussion information on maternal and infant prophylaxis. The information is also shown in Table 5*
Reviewer's report [3]

Title: Factors associated with HIV infection among children born to mothers on the Prevention of Mother to Child Transmission programme at Chitungwiza Hospital, Zimbabwe, 2008

Version: 2 Date: 18 June 2013

Reviewer: Lars ThoreFadnes

Reviewer's report:
The manuscript has several possibilities for improvement. Much of the findings in the article are known. The writing is acceptable, but the method and discussion sections need to be elaborated much.

1. Is the question posed by the authors well defined?
The objective of the researchers is stated quite clearly. However, it is not clear whether the methodology is capable of answering all the questions/objectives(e.g. whether immunization status influences HIV status). The first sentence “We investigated factors associated with HIV infection among children born to HIV positive mothers already on the PMTCT programme at Chitungwiza Hospital. “seems to cover what has been done in the article better. Thus, one options could be to delete the second sentence of the objectives (last sentence in the background section).

We feel as authors the case control study was adequate to answer most of our objectives but may not be adequate to answer the question posed by the reviewer. We have therefore deleted the second sentence of the objectives from the manuscript.

2. Are the methods appropriate and well described?
No, the methods need to be better described (see comments below).

We have revised the whole methods section so that it is clearer

3. Are the data sound?
Some of the stratification/categorization choices seem arbitrary and in some cases counterintuitive. As an example, in the list of independent risk factors breastfeeding is presented as a risk factor while breastfeeding for less than 6months is presented as a protective factor (see more comments below).However, it seems to be possible to improve this through revision.

We have made some revisions to this

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
The manuscript lacks sections on use of statistics, selection of the study participants (which time period, inclusion criteria etc), hardly has any discussion of limitations, were the respondents interviewed specifically for the study or as part of clinical setting, whether clinical records were used or whether it was a specifically designed form for the study etc. Were the women interviewed by the same personnel who counseled on e.g. breastfeeding? If so, such aspects need to be discussed in the limitations. The setting in terms of availability of antiretroviral treatment among mothers, nevirapine use during delivery etc could also be elaborated.
We have extensively revised the methods section to take into account the reviewer’s concerns. The respondents were interviewed specifically for the study and interviews took place in the hospital. The women were referred to counselors who work within the hospital. We have described the setting in terms of antiretroviral drug availability.

5. Are the discussion and conclusions well balanced and adequately supported by the data? The article could have had a better and richer discussion. This includes a more elaborated discussion on aspects related to problems with early weaning of breastfeeding (see reference Kuhn L et al. N Engl J Med 2008, complete reference later in review).

We have tried to enrich the discussion by reviewing more literature and including the data in the discussion of this report.

There are also several statements without source/reference (such as “The risk of MTCT through breastfeeding is cumulative. The longer the HIV-infected mother breastfeeds, the greater the additional risk of transmission through breastfeeding.” This is very likely to be true according to the literature, however please include a reference for statements that cannot be concluded from your study.

We have tried to reference most statements that cannot be concluded from our study.

The conclusion seems to also bring up aspects which are difficult to see as built on the findings. Why do you end up concluding “So we recommend that the ANC counselors encourage exclusive breastfeeding period for 4 months”?

We have revised the conclusion building on our findings.

6. Are limitations of the work clearly stated? No. The limitations needs to be further elaborated.

We have now included an elaborate paragraph on limitations.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? The article could have a better/richer discussion and background. I suggest that the following references could be considered to be referenced:

We have reviewed the suggested literature and included it in this manuscript

9. Do the title and abstract accurately convey what has been found?
The title is acceptable. The abstract could be improved according to the suggested revisions in the paper.

We have done some revisions to the manuscript in line with the suggested revisions

10. Is the writing acceptable?
The writing is generally acceptable.

Major Compulsory Revisions
See comments above related to particularly the methods section, discussion and conclusion. There are no descriptions of the regression analysis in the methods section. Is it stepwise forward or stepwise backward? There is no indication on which tools/programs that has been used. In the regression analysis, it is stated in the result section that “Further multivariate analysis (logistic regression analysis) was done to estimate the measures of association while simultaneously controlling for the confounding variables immunization and hospitalisation since infancy.” Was these factors found to be confounders or regarded as potential confounders?

We have revised this section to include the regression analysis done in the methods section. We have included the tools used and the software. We have also stated that we did stratified analysis to assess for effect modification and possible confounding.

Which factors were included in the stepwise model?

We included the following variables in the stepwise model: Maternal CD4 count, breastfeeding > 3 months, treated for an STI, full immunization status, nevirapine adherence, and exclusive breast feeding for ≤6 months, hospitalization, mixed feeding.
In the abstract it is written “being exclusively breast fed for less than 6 months” while in table 2 it is written “Breast feeding for # 6 months”. Please present the categories similarly. How is exclusive breastfeeding defined in this study? Is it based on 24-hour recall, 1-week recall, ever recall? Are medicines/vitamin supplements/oral vaccines “allowed” in the definition of exclusive breastfeeding?

-exclusive breastfeeding was defined as giving the infant only the mother’s milk for the first six months. Prescribed medicines/vitamin supplements/oral vaccines were “allowed” in the definition of exclusive breastfeeding and it was based on ever recall.

The list of independent risk factors presenting breastfeeding as a risk factor while breastfeeding for less than 6 months as protective factor seems to be a counterintuitive way of presenting data. Please rather use a reference category which is e.g. “no breastfeeding” comparing with “breastfeeding for less than 6 months” and “breastfeeding for more than 6 months”

We have revised the presentation of independent risk factors

Minor Essential Revisions
The presented adjusted odds ratios (aOR) are given with two decimals. This indicates higher precision of the estimates than what is observed. Thus, please have a maximum of two valid digits in the aORs (1 decimal in the aORs<10 and no decimals in the aORs>10).

We have revised the aORs as recommended

Similarly in table 1, with n of 60 in each group, the percentages could without decimals.

We have revised the decimals for the percentages

Discretionary Revisions
The following sentence could be simplified: “In spite of all these efforts to reduce the risk of mother to child transmission of HIV, 25% of the children, born to HIV positive mothers, have themselves tested positive to HIV after 18 months despite having been on the PMTCT programme.” I suggest: “Among the children born to HIV positive mothers participating in the PMTCT programme for 18 months, 25% tested positive to HIV.”

We have revised the construction of the statement accordingly

Why introduce a new abbreviation “maternal-infant transmission (MIT)” when “Mother-to-child transmission (MTCT)” is familiar to much of the clinical and scientific audience in the topic of paediatric HIV.

We have revised and used the abbreviation that is familiar to much of the clinical and scientific audience.
Once more the authors of this paper declare no competing interests and this study has not been published elsewhere. We hope this article will be of interest to your readership.

Sincerely,

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