Author’s response to reviews

Title: Incidence, prevalence and associated factors of mother-to-child transmission of HIV, among children exposed to maternal HIV, in Belgaum district, Karnataka, India

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Author’s response to reviews:

Editor Comments:

1) Ask a highly qualified native English speaker in the field of medicine or a copyediting company to edit your manuscript based on the latest version for proper English language, grammar, punctuation, spelling, and overall style to reach the textual level of publication.

Three of the co-authors are well qualified in the filed of medicine.

2) The title in the manuscript should match the title in the Editorial system.

Not able to understand this comment. We changed the title as per the editorial system in the abstract submission page.

Reviewer reports:

Marta Andres Miguel (Reviewer

Abstract:

Page 2 Line 9: What is it meant with cumulative prevalence rate?
Response: The rate was calculated based on the total number of HIV positive children at different ages. Thus, we termed it as cumulative prevalence. However, we have now changed this to prevalence rate in the article, as it represents prevalence at that point in time.

Page 2 Line 16: Could you indicate the hazard ratio for Nevirapine administration compared to the other categories, as shown in line 14 for breastfeeding?

Response: We have included the adjusted hazard ratio for the Nevirapine in the abstract.

Background:

Page 3 Line 9: Please, include a reference for "3% of all new infections"

Response: The estimated number of new infections in 2015 is 86000 including 10400 among children (Mid Term Appraisal Report 2017). This works out to 12% of all new infections. We have added the reference for this.

Page 4 Line 48-50: It is not clear to me where the difference between 0.75% HIV prevalence among ANC attendees and 0.21% among PPTCT attendees comes from. Are they different populations? Could you explain better?

Response: ANC attendees refers to HIV sentinel surveillance results. This is restricted to Government hospitals at the district and one sub-district level. These centres are also Anti-retroviral Treatment centres, and could therefore have larger proportions of HIV infected women who attend these clinics for free ART. PPTCT attendees captures HIV prevalence among all ANC who attend antenatal services including district, sub-district and primary care facilities, both public and private.

Methods:

Page 5 Line 34: Please, be consistent in using "breastfeeding" or "breast feeding".

Response: We are consistent in using breast feeding.

Page 5 Line 37: When was the questionnaire performed? If the questionnaire was performed at different times after delivery, this could lead to recall bias. When was the information about the breastfeeding practice collected, as this cannot be collected after delivery? Please, provide more detail about how was the information collected along the study.

Response: The results on breast feeding are captured at fixed intervals following delivery, usually within the first week after birth, between 6-10 weeks after delivery, 6-9 months after delivery and once every quarter 12 and until 24 months after delivery.

Results:

Page 7 Line 11: When was the media age at which children tested HIV positive?
Response: The estimated median age at which children tested HIV positive is given in the result section.

Page 7 Line 42: Would it be possible to show if under the category "either mother or baby were given Nevirapine", it was the mother or the child who received the treatment? Does this have any influence in the outcome variable?

Response: Actually, there was only 2 cases where mother only was given Nevarapine. In the remaining 56 cases the baby alone was given Nevarapine. So, we decided to combine these two.

Page 8 Line 7-16: It would be helpful if the authors present the values (cumulative incidence rates) for the different categories in the text.

Response: This is presented as per the suggestion.

Page 8 Lines 31-47: In this paragraph, values (percent) are shown for some categories but not for others. Please, be consistent. Also, it is not clear where HIV prevalence of 7.8% among exposed babies comes from. It would be helpful if authors could show the numbers of HIV infected and exposed babies for the different categories in the tables to facilitate understanding.

Response: As suggested, we have provided the percent value. Similarly, we have provided the number of infected babies in each category.

Page 9 Line 12: What about the age of the mother? This is also associated with MTCT risk.

Response: We have mentioned the association of age of the mother in the text.

Page 9 Line 19: "When controlled for other risk factors". This is always the case for multivariate analysis and for the results presented in this paragraph, so I would delete this sentence.

Response: As suggested this has been deleted from the sentence.

Discussion:

Page 9 Line 43: I think that "during the year" and "between 2011 and 2013" might be redundant. Or "during the years between 2011 and 2013".

Response: The sentence has been changed

Page 9 Line 57- Page 10 Line 7: The authors provide valuable information about the results in other studies, but do not discuss where the differences in MTCT might come from. I think this section would benefit from a brief discussion about these differences.

Response: This is now included in the discussion in response to both the reviewer’s comments.
Page 10 Line 10: In Table 4, also the age of mother >30 is associated with MTCT, why do the authors do not comment on this?

Response: As suggested, we mentioned the association of age of the mother in the text.

Page 11 Line 15: I would rather say "the present study showed a tendency of mother who started ART more than 90 days prior to delivery to…" As the differences across the status of ART initiation by mother are not significant.

Response: As per the suggestion, the sentence is modified.

Page 11 Line 43: As I understand from what the authors say in the background section, PPTCT interventions in India changed in September 2012 with the introduction of triple drug ARV regimen. As this change occurred during the study, it complicates the interpretation of the results as the study population is not homogeneous. I think it should be listed as a limitation of the study and discussed as to how this might have influenced some of the results on the effect of ART initiation on MTCT.

Response: This is included as one of the limitations of the study.

Abbreviations:

Please, include ARV. "ART" stays for anti-retroviral therapy.

Response: As suggested this abbreviation has been included

Tables:

I think the tables would benefit from including the number of individuals in the numerator for each of the categories.

Response: Modified the tables as per the suggestion.

Amanuel Kidane Andegiorgish, MSc (Reviewer 2): Thank you for the opportunity to review the Title

The title should and must be very specific. In your study you have used two things,

It implies overall child bearing mothers in Belgaum district. Suggestion "Incidence and associated factors of mother-to-child transmission of HIV, among …. in Belgaum district, Karnataka, India

In your title there is no point indicating prevalence, but you have added table of prevalence.
Response: The title is now changed as “Incidence, prevalence and associated factors of mother-to-child transmission of HIV, among children exposed to maternal HIV, in Belgaum district, Karnataka, India”

Abstract

Page 2, Line 50. All Belgaum resident pregnant women who tested HIV +Ve, were included. How representative this is to the population of study area? This is facility based list study and not considering home delivery.

Response: The proportion of pregnant women attending ANC clinics in the Belgaum district is more than 95%.

Page 2 line 50 and page 7 line 57; the result in the abstract and the main text are different. One is starting with mothers and one with children. Better to start with main objective outcome.

Response: This has been corrected.

Page 3, line 16. The risk of HIV transmission has significantly reduced if the mother or the baby has received Nevirapin after delivery, how strong, use OR?

Response: We have included the adjusted hazard ratio for the Nevirapine in the abstract part of the text.

Page 3, line 21. Your study highlighted that exclusive breastfeeding beyond 26 weeks is a risk for vertical transmission of HIV. How many samples were in exclusive breastfeeding post six months? How trustworthy is this to conclude considering your study design, sampling method and sample size? What further action do you recommend to confirm this?

Response: The details of the number of samples included beyond 26 weeks are now included! We have mentioned that this finding is suggestive, not conclusive!

Page 3, line 26-41. ….limiting exclusive breast feeding up to 26 weeks, among HIV infected mothers is critical to reduce incidence of paediatric HIV in India. How generalizable is this study to paediatric HIV in India?

Response: This has been addressed in the discussion section.

Page 3, line 34. Key words; would be better to include prevalence, Nevirapin

Response: Added prevalence and Nevirapine as key words.

Background

Page 4, line 6 the Abbreviation of HIV would be better if explained in the first statement and use HIV in the preceding.
Response: We have expanded the abbreviation of HIV in the first statement as indicated.

Page 4, Line 6-11 and Line 18-23. No citation where this information is from.

Response: Citation is Added for this as per the suggestion

List of Abbreviations: not given for ARV.

Response: Abbreviation added for ARV

Page 5 line 14-17, to examine the incidence, prevalence and role (increase HR) of associated factors. Is this role, qualitative or quantitative? How would you estimate it?

Response: We used quantitative measure and not qualitative measure. The details about the measurements are provided in methods section.

Page 5 line 19-21. You mentioned "Previous studies in India, were either confined to a single facility or assessed the risk among urban dwellers only" How could your prove your study is encompassing both urban and rural residence besides facility based?

Response: The address of residence of the participants indicates that it is representative of both rural and urban, in expected proportions within the district. Also we used the information from health facilities form both rural and urban areas to identify the HIV positive mothers.

Page 5 line 49-50. In reference to citation no 20, you have stated that in 2012, HIV sentinel surveillance data indicated HIV prevalence of 0.75% among ANC attendees and 0.21% among the PPTCT attendees. How comparable is your study findings with this result? And why such a big difference?

Response: This data is related to HIV prevalence among pregnant women from two different sources of data from the public system in the district. The difference between these two data sources is explained in the text.

Page 6, Line 15-18 (Recruitment of study subjects). A similar previous study was done among women in River State Nigeria. Why not you use that proportion for estimation of the variable of interest in your study?

Response: We are unable to understand the comment. The referenced study was published after the study proposal was approved. The proportion for the estimation of variables were determined in accordance with the guidance from the Project Advisory Group.

Page 6. Line 32-34. Information on Date of HIV testing of mothers should come first of Date of start of ART.

Response: As per the suggestion, we mentioned first date of HIV, followed by date of start of ART.

Response: We mentioned the NACO document for EID testing guidelines dated 2010 in the text and also in the reference.

Page 6. Line 39-44. DNA PCR and Antibody Tests were used to diagnose children with HIV. However, from HIV positive children who did not have antibody, further tests were needed using RNA.

Response: We have not done any additional testing. This is as per NACO guidelines

Page 6. Line 44. The last test of Antibody testing was done at 18-24 months of age. Subjects recruited on may (end of study) will have 16 maximum months. How this is done?

Response: We used the survival analysis, the children who are not completed the study duration, due to lost to follow-up, or not completed the age criteria are considered as censored cases after the latest test conducted.

What is the proportion of the studied pregnancy of all pregnancy in the study area?

Response: Overall, 0.15% of about 0.11million pregnancies estimated in the district annually were studied. This represents about 80% of all estimated HIV pregnancies in the district annually.

Methodology

Page 6, line 6. A cohort study was designed, how? Do you have control group?

Response: We don’t have a control group. As mentioned in the methodology section it is a follow-up study of HIV pregnant women in the district and followed them at regular intervals. During the follow-up period HIV testing was carried out as per the EID criteria at various time points.

What is the probability of overall pregnant women to come to the health facility for ANC and pregnancy women who have knew their HIV status prior to pregnancy to come for ANC?

Response: As cited in the article [reference no. 35] 95 percent of the pregnant mothers received at least three or more antenatal check-ups in Belgaum district. However, we don’t have the information on the percentage of pregnant women knew their HIV status prior to pregnancy to come for ANC. However, our data suggested that 21% of the women knew about their HIV status prior to pregnancy.

Page 6 line 6-8. Study subjects were recruited from 1st January 2011- 31st May, 2013 and were followed un Nov 30, 2014. Those recruited on May 2013 will be followed only for 15 months?
Response: Since, we used the survival analysis for the estimation, such babies will be considered in the analysis as censored or HIV positive cases, until their last test date or until death date, if died or date of testing positive, if found HIV positive.

Page 6, line 46-48: Data Collection: No information regarding to data collectors as well as training related to the objective of the study.

Response: This information is now included in the methods section.

Page 6 line 24 "Consent was sought from all the eligible women included in the final list" would be better to bring in the ethical statement.

Response: As suggested, this sentence is now deleted and is included under the ethical approval.

Page 6, 39-44. Why three different blood tests, and what is the criteria of classifying positive for HIV baby based on the outcome (if one, if two or all three positives).

Response: Blood tests are done at three different time points (or different age of the bay) as per the EID protocol. We have considered the child to be positive, when found HIV positive at the earliest test.

Page 6, line 20. How many mothers were excluded due to duplication and movement to other places? HIV+Ve people are more likely to change places from their origin.

Response: About 15% of the crude line list was removed due to duplication or non-resident status within the district and 5% of those eligible for the study did not provide consent for recruitment.

Page 8. In your abstract method, there is no information regarding censoring.

Response: We included the information about the survival analysis that consider censoring of the observations in the abstract section.

Page 8 line 2 only 454 babies were tested for HIV at least once. But your result in the abstract seems calculated from the "487 children followed up, the cumulative incidence rate by 24 months of age was 4.8 per 1000 person months" How?

Response: The analysis includes all the cases irrespective of tested or not. As indicated in the text there were 23 babies who died before any HIV test. In the analysis these babies were considered until the age at death and censored at this point of time. For the other 10 children who were lost to follow-up, we considered them until 42 days (around 1.39 months), as suggested by the Project Advisory Group, and censored them at this point of time. So, the analysis included all the 487 babies, irrespective of whether they were tested or not.
Page 8, line 1. Insert Cumulative incidence of MTCT as subheading…(same as per the format of the journal)

Response: We have added the subheading as per the suggestions.

Page 8, line 7-9: by the age of 24 months 38 babies were identified as HIV positive by the three tests. How many of them were exclusive breastfed more than 26 months?

Response: Out of the 38 babies who were identified to be HIV positive, 11 babies were found to be exclusive breastfed for more than 26 weeks.

Page 8, line 7: you said 23 babies were not tested due to death, again in same page 8, line 14: 33 babies died, does not this contradict?

Response: There is no contradiction, 33 babies died. In the text we have already indicated that 10 of the babies who died were tested for HIV at least once before death and 23 babies were not at all tested for HIV.

Page 8, line 14: the prevalence of HIV among died babies was 10%. Can we say the prevalence of death was higher among HIV positive babies? If it is, probably many children were dying before coming to health facility and HIV test?

Response: This may be true. However, we cannot comment or document this aspect in the text. This is because majority of the babies who died do not have a test result. The number of samples tested among the babies who died are only 10.

Page 8, line 31-38: Mothers have started ART on different time schedule. Was it on the mother choice, decision by the health care professional or by the investigator?

Response: The decision to start ART is guided by the NACO protocol and the clinician at the ART centre, not the investigator. It is also depend on whether mother interested in initiating the ART.

Page 8, line 17-21. What is the relevance of stating time of death of the 33 died children in your result.

Response: We have provided this information, in order to provide readers with an idea about the distribution of death according to age at death.

Page 8, line 38. Only 9% mothers initiated ART after the delivery. This should be 40 out of the total mothers of tested babies. Because at last we want to see how timing of ART initiation correlate with MTCT of HIV, which is our objective. The table need to be reconsidered again using these assumptions.
Response: We have provided both the number and the percentage in the table. 45 mothers were initiated on ART after delivery.

Page 8, line 45. Not around. One-third of the babies were not breastfed at all.
Response: Corrected as per the suggestion.

Page 9, 7-12…….. their HIV status prior to pregnancy, compared to mothers of their counterpart.
Response: Corrected as per the suggestion.

Page 9, line 32. Prevalence of HIV transmission in the study area. Commented for consideration of prevalence starting the title of the study. Justification needed regarding the relevance and strength of prevalence information in this report.
Response: We have changed the title as per the suggestion.

Page 9, line 45-47. Redundancy with line 33 above
Response: This has been addressed.

Page 9 line 57. You have mentioned >24 months breastfeeding and Naviparin has a strong risk factor for HIV transmission, and on page 10, line 2-10, Naviparin has reduced risk of HIV (AHR = 0.25 and 0.12)?
Response: The sentence has been deleted from the text.

Result

Your study is about Incidence and associated factors of mother-to-child transmission of HIV xxx district. And it is known that HIV transmission from mother to child is influenced by the CD4 count as well as Viral load of the mother, how did you try to control the potential confounding for your association study.

Response: We were not able consider for the CD4 count and Viral load as confounding factors because information on CD4 was missing for a large proportion of patients. At the time of this study, viral load estimations were not included in NACO protocol. We have indicated this as a limitation of the study.

Table 1. Use same format like table 2 and 3, 2nd column number of children and 3rd column percent.
Response: As suggested the column values are shifted.

Table 2: How was the cumulative incidence rate calculated to handle censored information?
Response: We have included this in the data analysis part of the methodology section.

Page 8, line 1-5. We estimated the cumulative incidence rate (CIR) of MTCT per 1000 person months by age 24 months. We used survival analysis to include the lost to follow-up cases to estimate CIR and the results are presented in Table 2. Better to bring to the methodology section. (I think already mentioned so don't do redundancy).

Response: We have deleted the sentence and mentioned this in the data analysis part of the methodology section.

Page 8, line 31-43. The first statement is about initiation of ART, and the second statement is who took Nevirapine and as prophylaxis. Are they different? If not reconsider the term "however".

Response: This has been addressed.

Table format follow the BMC format

Response: Changed the format of the table as per the BMC.

Page 10, line 14-17. and page 12, line 38-42. In your literature you have mentioned that cesarean section reduce risk of HIV 1-2%, but in your study not, discus why?

Response: The sentence related to the query is written as “Transmission rates of 1–2% have been reported in studies from developed countries, owing to effective ART, appropriate management of delivery, and avoidance of breastfeeding”. In the results presented in the paper, caesarean section implies a reduction in the MTCT transmission, but this the association is not statistically significant. This could be because of the small numbers who underwent caesarean section. The small numbers limit the estimation of the risk of transmission.

Page 10, line 38-52, this part of the discussion has not logical order with the main findings of your study. Discus in the discussion section not evaluate.

Response: This has been addressed.

page 10 line 51-52. What does it mean cohorts of babies gathered through a systematic approach? How does it apply with your study?

Response: Systematic approach, here means that we have meticulously obtained the list all HIV positive mothers in the district without omitting anybody. This way it includes almost all the mothers in the district who were found to be HIV positive during the study period. We also deleted the duplicate observations and followed the cohort of all mothers and babies recruited for the study at regular intervals of time. The word systematic has been deleted as it is ambiguous.
Page 11, line 9-12. The study identified two factors, breastfeeding and Nevirapine prophylaxis, to be associated significantly with the MTCT among HIV exposed children by the age of 24 months. I think the association is in different way, needs revision.

Response: This has been modified.

Page 11 line 52. How many children have received ART after delivery and were protected from MTCT?

Response: As per our sample, in total 460 babies (include 404 babies both baby and mother) had received Nevirapine. Out of this 32 were identified to be HIV positive and correspondingly 428 were protected from MTCT.

Page 11 line 1-12. Is not your objective to compare, How can you suggest ARV should be changed by ART?

Response: We are not suggesting that ARV should be changed by ART in the lines indicated.

Page 13, Line 59. And page 14 line 1-7, are not your study objectives.

Response: The indicated sentences are provided in the article only to provide information about the current guideline regarding the breastfeeding to babies by the mothers of HIV positive.

Reference:

Majority of the articles you have cited are old, it would be better to use latest reference to make easy for comparing the knowledge in practice. There are many updated information’s like "BMC Infect Dis. 2018; 18: 216. doi: [10.1186/s12879-018-3126-5, PMCID: PMC5946547 PMID: 29747581]."

I have not seen a single reference similar to your topic. Is this because of uniqueness of your topic or not? Suggestion read this paper (THE LANCET * Vol 360 * August 3, 2002 * www.thelancet.com ) . All literature close similar to your study are old enough why?

Response: The suggested paper in the Lancet was studied. The context was South Africa and the study reported only estimates of the prevalence of HIV-1 among infants. It is also not clear whether they are carried out repeat tests or not. It is not clear until which age children are included in the study. We used PubMed, Google Search, Popline data bases to get close to the research that provides information about association between MTCT and risk factors. We have referred the papers which are available to us through the search mentioned. As much as possible we have quoted the studies which were relevant to our topic. Some of them may be old. But most of the research quoted are after the year 2000. The reference quoted by the year in the paper was given below:
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No uniformly reported. Example Ref. No 13 and 12, 26, 27; the name of authors to be listed should be similar.

Response: We have examined this and have now uniformly reported this.

Ref. No 29. This is not WHO guidelines of ART administration on CD4 count. Check it again.

Response: We did not mention it as WHO guideline. For pregnant women, NACO had instituted a ‘Test and Treat’ policy, if detected HIV infected, irrespective of CD4 count.