Author's response to reviews

Title: A retrospective study of Human Immunodeficiency Virus transmission, mortality and loss to follow-up among infants in the first 18 months of life in a prevention of mother-to-child transmission programme in an urban hospital in KwaZulu-Natal, South Africa

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Version: 6 Date: 28 August 2012

Author's response to reviews: see over
Dear Ms Crow,

We thank the reviewers for their comments on our manuscript titled “A retrospective study of Human Immunodeficiency Virus transmission, mortality and loss to follow-up among infants in the first 18 months of life in a prevention of mother-to-child transmission programme in an urban hospital in KwaZulu-Natal, South Africa” Manuscript ID MS: 6911790147000691. We have attended to all comments, and have improved the manuscript as a result.

Below, we describe how we have taken the comments into account in the revision of our manuscript. Our responses are italicized. References to specific pages in the revised version are shown. The revised manuscript conforms to the house style of your journal.
Author’s response to reviews

Title: A retrospective study of Human Immunodeficiency Virus transmission, mortality and loss to follow-up among infants in the first 18 months of life in a prevention of mother-to-child transmission programme in an urban hospital in KwaZulu-Natal, South Africa Manuscript MS: 6911790147000691

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Version: 2 Date: 28 August 2012

Author’s response to reviews: see over
Point-by-point response to the reviewers concerns.

MS: 6911790147000691, A retrospective study of Human Immunodeficiency Virus transmission, mortality and loss to follow-up among infants in the first 18 months of life in a prevention of mother-to-child transmission programme in an urban hospital in KwaZulu-Natal, South Africa

Reviewer’s report 1

Version: 1 Date: 23 June 2012

Reviewer: Karl-Gunter Technau

Reviewer’s report:
The manuscript addresses the problem of loss to follow-up, mortality and HIV transmission in the context of the South African PMTCT programme in a hospital that is state subsidised. Records were reviewed for women assessed and delivered and infants born in a 13 month period in 2008/2009. There is a high Caesarean rate in this cohort and guidelines are slightly different to national guidelines yet evidence based. Transmission is documented (2.7%) for the six week time point but there is little follow-up to 18 months which makes assessing transmission at this point more difficult. Mortality is noted as 1.7% at 6 months while loss to follow-up is high with the highest rate occurring in the early months of life. Late antenatal booking is noted to be a factor. The authors conclude that it is important to investigate loss to follow-up in this context. The manuscript is relevant to paediatrics and is especially important in the context of the changing South African PMTCT programme where infant follow-up is vital and challenging in the context of high and changing rates of breastfeeding. Addressing the problem of loss to follow-up is therefore useful and it is a problem that many hospitals and clinics will be able to identify with. The methods used by the authors are appropriate and the data is well presented.

Response: Thank you to the reviewer for these encouraging comments and for a thorough review of the paper.

Minor Discretionary Revisions:
1. When reading the paper, the results and conclusions of the abstract should possibly reflect the effect of late booking.

Response: We have added the following line in the results section of the abstract (page 2) “In Cox regression analysis, late antenatal attendance (≥ 28 weeks gestation) relative to attending in the first trimester was a predictor for infant LTFU (adjusted hazards ratio=2.3; 95% CI: 1.0 to 5.1; p = 0.044). We have also changed the conclusion to reflect the effect of late booking “The LTFU of infants born to women who attended antenatal care at 28 weeks gestation or later emphasizes the need to identify late antenatal attendees for follow up care to educate them regarding the importance of follow up care for themselves and their infants.”
2. The 135 women who received PMTCT prophylaxis (as opposed to ART for life) include 14 women with #other# in Table 1. This does not come out clearly in the text and would almost suggest when reading it that they did not receive an intervention. This could possibly be clarified.

Response: Thank you for this comment. The results regarding the PMTCT prophylaxis categorized as “other” has been reviewed. The fourteen women classified as “other” were incorrectly classified in the original submission. Five women received either ART for life, and nine women received PMTCT prophylaxis (zidovudine, lamivudine, and efavirenz from 28 weeks). The results section of the text (page 10) and the table (page 23) has been revised to reflect these changes.

3. Was there any maternal morbidity or mortality noted or deaths of mothers in the follow-up time?

Although this is not the purpose of this study, it may have an effect on infant follow-up.

Response: We have added the following lines to the results section (page 9) “Twelve of 127 (9.4%) women with data had pulmonary tuberculosis and were receiving treatment. There was only one maternal death during the study period. The cause of the maternal death was reported as disseminated Kaposi’s Sarcoma.”

4. The authors could possibly comment on the high caesarean section rate which may have helped achieve the low transmission.

Response: We have revised the discussion section to reflect the role of the high caesarean section rate on HIV transmission risk on page 13, “In developed countries vertical transmission of HIV to infants occurs in 1-2% of pregnancies in HIV infected women, achieved through a combination of interventions, including antiretroviral therapy regimens that optimally suppress viral load, elective Caesarean section and complete avoidance of breastfeeding. In developing countries the caesarean section proportion ranges from 3% to 12.6%. The high proportion of caesarean sections at McCord Hospital may reflect the ability of the women in this setting to choose the best possible care for their infants and the hospital's capacity to deliver a comprehensive package of interventions to reduce the vertical transmission of HIV.

5. In the supplementary table presenting the Cox analysis, I assume #n# is for the LTFU group and the #Number# for the whole group. This could possibly be labelled better.

Response: Thank you. The supplementary table has been revised with “Number” changed to “Live born infants” and “n” changed to “Infants LTFU”.

Minor essential points to be addressed:
1. Please check the IQR#s. They seem to mostly be (Min Max) values. E.g.CD4 count 308 cells/mm3 (IQR: 17 to 962 cells/mm3) in the text while in the table 58.8% of women fall between 200 and 499.

Response: Thank you. All the IQRs in the results section (table 2 and text) has been revised as appropriate.
2. The number of 166 in care at six months in the abstract and the emphasis on 155 in care beyond 28 weeks does not fit together and may need to be changed in the abstract, though both numbers are probably accurate, they seem to be confusing.

Response: We agree that this line in the abstract seems to be confusing. We have revised the abstract (page 2) as follows “Of 260 infants, 155 (59.6%) remained in care at McCord beyond 28 weeks: one died at < 28 days, three died between one to six months; 34 were LTFU within seven days, 60 were LTFU by six months.”

3. When referring to Reference 10 (Jones et al) it may be important to mention that the study was conducted in the time when routine PCR testing at six weeks was not yet part of national guidelines and many sites were doing ELISA tests at 12 months.

Response: Thank you. We have added a line in the text (page 4) to reflect the testing guidelines at the time the Jones study was conducted “At the time this study was conducted, the national guidelines in South Africa did not include routine HIV testing for infants at six weeks and recommended testing for infants at 12 months of age.”

4. There is a #be# repeated in the third last line of page 12.

Response: Thank you. This has been corrected.

Level of interest: An article of importance in its field

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.
Reviewer’s Report

Major Compulsory Revisions
This is an article of importance considering the high prevalence of HIV among women of child bearing age and that mother to child transmission can be reduced drastically due to provision of ARVs which need close monitoring and compliance.

Response: Thank you for this encouraging comment and for your detailed review of this paper.

The paper is well laid out but there is need to revisit the discussion part which is not supported by current literature. It has turned out to be a narrative interpretation of the results without really comparing it to literature and pointing out the key issues of loss to follow up.

Response: The discussion section has been revised and includes analyses of relevant literature on loss to follow-up in PMTCT programmes. The following sentences and paragraphs have been included in the discussion on pages 13 and 14, respectively:

“A similar finding was noted in a PMTCT programme at a centralized hospital in Malawi [14]. The authors suggested that the LTFU of mother-infant pairs may have been due to women from rural areas returning to their peripheral clinics following delivery [14].

“In prior studies, poor socio-demographic circumstances were associated with patient attrition. In Malawi HIV-exposed infants born to parents who were less educated and in farming occupations were more likely to be LTFU [11]. In our multivariable model, there was no association between socio-demographic characteristics and infant LTFU (maternal employment and marital status). Since the parental level of education was not routinely collected at the time this study was conducted, the association with LTFU could not be assessed. In the Ugandan study lack of understanding of the importance of follow-up was noted as a reason for attrition [12]. In Johannesburg, maternal unemployment, geographical relocation and lack of paternal support were noted as reasons for poor retention [10]. Maternal education regarding the importance of follow-up care for their own and their infants’ health may improve patient retention and facilitate early diagnosis of infant morbidity and HIV transmission risk.”

“This study demonstrated that relative to infants of HIV-infected women with CD4+ counts 200 cells/mm³ or less, infants born to mothers with CD4+ counts above 200 cells/mm³ were more likely to be lost to follow-up. This finding was not statistically significant. Maternal well-being may be a risk factor for poor retention in our setting as mothers do not perceive themselves or their infants to be at risk for disease. These mothers may be less likely to seek health care. A similar correlation between infant wellbeing and loss to follow-up was shown in a study in rural Uganda, where infant illness was a protective against loss to follow-up in the PMTCT programme [12].”
In the results section where data is not shown; there is no need to repeat the phrase several times rather spell out the results and at the end of the paragraph state that data is not shown.

Response: Thank you. The results section has been revised as suggested where data is not shown.

There is also need to consult the statistician on the results and their presentation e.g. for the HIV overall transmission the total then n=6. This can be rephrased after consulting.

Response: Thank you. The sentence has been changed (page 11) to “At 6 weeks 220 (83.0%) infants returned for HIV testing by PCR, and 6 (2.7%, 95% CI: 1.0% – 5.8%) were found to be HIV positive.”

Generally the sentences are quite long especially in the results section where it becomes difficult to follow and the discussion too where one sentence is up to or more than 3 lines!

Response: We agree that the sentences are wordy. We have shortened the sentences in the results section and the discussion.

Minor Essential Revisions
There is a reference of Giddy J... which i feel should be quoted as a number.

Response: In keeping with the house style of the BMC Pediatrics, the reference re Giddy is a personal communication and was therefore not included in the reference list.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that i have no competing interests

We have carefully responded to the reviewer’s comments above and have indicated the page where changes were done in the revised manuscript.