Author's response to reviews

Title: Associations between gestational anthropometry, maternal HIV, and fetal and early infancy growth in a prospective rural/semi-rural Tanzanian cohort, 2012-13

Authors:

Amanda L Wilkinson (alw252@cornell.edu)
Sarah H Pedersen (sp729@cornell.edu)
Mark Urassa (urassamark@yahoo.co.uk)
Denna Michael (dennamichael@gmail.com)
Jim Todd (jim.todd@lshtm.ac.uk)
Safari M Kinung’hi (kinunghi_csm@hotmail.com)
John Changalucha (jchangalucha@yahoo.com)
Joann M McDermid (jmm585@cornell.edu)

Version: 3
Date: 15 July 2015

Author’s response to reviews: see over
Dear BMC Pregnancy & Childbirth Editors:

We are grateful to the reviewers for their thoughtful comments and thank you for the opportunity to submit a second revision of our manuscript entitled, “Gestational mid-upper arm circumference and birth or early infancy anthropometrics in HIV-exposed and unexposed infants: a prospective cohort”.

We have summarized point-by-point responses to each reviewer comment indicated below, as well as noting corresponding changes in the revised manuscript.

Sincerely,

Joann M. McDermid

Reviewer: Mathurin Tejiokem
Reviewer’s report: Authors have responded to the reviewer’s comments in a satisfactory manner. The manuscript now read more clearly with different definitions and precisions provided. But, i will like again to comment on the source population for inference. In my previous review, i requested some informations on that issue. For example, from March to November 2012 in Kisesa health center - how Many pregnant women were received? Among them, how many were HIV positive for authors to include 44 pregnant women - concerning the HIV negative women, no information was provided on selection procedure Lastly, in figure 1, authors should present data according to HIV status to improve understanding

Unfortunately, the total number of pregnant women attending Kisesa Health Centre and the rural health dispensaries during this study period is unknown. The study recruitment procedure for HIV-positive and HIV-negative women is described in Lines 98-104 and 118-21. All HIV-positive mothers meeting eligibility criteria specified in the text were invited to participate, likewise, all HIV-negative mothers were invited to participate who met the eligibility criteria with no other selection criteria applied except that they were recruited in a 2 to 1 ratio to HIV-positive mothers. The “rate-limiting” factor in the recruitment strategy was the number of eligible HIV-positive mothers. Figure 1 has been updated to include recruitment and follow-up according to maternal HIV-serostatus.

Reviewer: Andreas Chiabi
Reviewer’s report: Minor Essential Revisions Comment 6 under methods: The Ethical aspect is good and well said, but should be precised in the text
The following text has been added to the Methods section: “Participants in this observational study that were identified as malnourished or requiring additional clinical follow-up for any condition were referred via the study physician who facilitated liaison and linkage with the main clinical services of Kisesa Health Centre” (Lines 108-10)
Comment 104 under methods: The fact that the HIV confirmation test was not done at the end of pregnancy or to the best in the delivery room should be put in the text as a selection bias. The following text has been added to clarify: “It should also be noted that pregnant women were
tested for HIV at study entry, and it is possible that HIV-negative women may have subsequently seroconverted. The likelihood of subsequent seroconversion is unknown as standard of care includes a single maternal HIV-test.

Reviewer: Kathleen Powis
Major Recommendations:
1. In the CONCLUSIONS section of the ABSTRACT, it is stated that “HIV exposure was associated with poorer anthropometry through 6-months despite improving antiretroviral access.” First, 55% of the women in the cohort received AZT monotherapy, not triple therapy. Secondly, there was no analysis to discern whether in utero exposure to triple antiretroviral resulted in poorer growth outcomes compared to monotherapy. Therefore, reference to improving access to antiretrovirals in the CONCLUSION of the ABSTRACT should be deleted, as it will only serve to misinform a reader who may think that this quantitative analysis was conducted in the current study.

We have changed this sentence of the abstract to read: “In this rural and semi-rural setting, HIV-exposure was associated with poorer anthropometry through 6-months despite maternal antiretroviral access” (Lines 51-2).

2. In the CONCLUSIONS section of the ABSTRACT, the closing sentence states “Further research is needed to establish gestational MUAC reference ranges and to define interventions that successfully improve MUAC during pregnancy.” As noted in my introductory paragraph above, I agree with the need for appropriate maternal gestational MUAC cutoffs. However, merely calling for interventions that improve MUAC will not go far enough. Interventions must demonstrate that improved MUAC improves growth outcomes. This study showed that a higher MUAC resulted in better infant growth outcomes. However, it did not demonstrate that changing MUAC during the course of a pregnancy results in improved infant growth outcomes that approach normalized z-scores. Future research designed to investigate if improving MUAC during pregnancy results in improved infant growth outcomes should be pursued; however, it was not within the scope of the current observational study to answer this question directly.

3. In the METHODS section beginning at line 124, there is mention that the sample size recruited exceeded that required to detect various means and standard deviations. However, it does not include the level of power that existed for each of these measures. Please include. The power is included in the text Line 122.

4. In the METHODS section beginning at line 148 on line 8, it is indicated that the HIV-exposed infants received daily nevirapine for six weeks. There is no mention made in the DISCUSSION section of this paper as to how nevirapine exposure may have influenced growth outcomes. Please comment. This study was not designed to investigate the impact of antiretrovirals on growth among HIV-exposed infants and nevirapine adherence was not ascertained; therefore, we are unable to speculate on this.
5. In the RESULTS section starting on line 222 of page 12, it is indicated that characteristic of 44-HIV-positive and 70 HIV-negative participants are summarized in table 1. However, table 1 contains characteristics of the women and their infants. Please replace “participants” with “women enrolled in the study and their infants” or some other statement that is clearer about the contents of table 1.
Modified as suggested, Lines 223-4.

6. In the RESULTS section, beginning at line 223, it is indicated that women did not appear to be at “nutritional risk” according to body mass index as the overall cohort mean was normal. First, “nutritional risk” is a subjective term that is inappropriate for a RESULTS section of a manuscript. Secondly, means do not define the BMI of all women in the cohort. There may have been some women with BMIs in pregnancy of 18 kg/m2 or less, which would be very concerning. It may be more appropriate to make a statement such as “Mean BMI did not differ significantly by maternal HIV status.”
Modified as suggested, Lines 224-5.

7. The eligibility for study enrollment is states as being < 36 weeks. Yet, on page 12 of the RESULTS section starting at line 226, it is stated that the range of gestational ages for enrollment spanned form 13 to 39 weeks. How can this be?
We have changed the description of the eligibility to no longer include “<36 weeks gestation” since women were indeed recruited through estimated gestational age 39 weeks (Line 114-8).

8. In the MATERNAL CHARACTERISTICS portion of the RESULTS section on page 12, starting at line 234, it is stated that HIV-positive women were not different from HIV-negative women in their “overall health” according to anthropometric measures. This is a subjective statement. While anthropometric measures are associated with health, to take mean anthropometric measures and conclude that lack of difference in means translates into comparable health is inappropriate in general and specifically in the results sections. It would be appropriate to state which mean anthropometric measure did not differ statistically between HIV-positive and HIV-negative women.
Modified as suggested, Lines 235-6.

9. In the MATERNAL CHARACTERISTICS portion of the RESULTS section on page 12, starting at line 243, it is stated that timing of AZT initiation in pregnancy for PMTCT “varied considerably”. Again, this is a subject characterization that is inappropriate for a RESULTS section of a manuscript. Furthermore, 80% of women initiated in the second trimester, the period at which most women had their first prenatal visit. Therefore, the subjective characterization of timing of AZT initiation is even more inappropriate. It is appropriate to merely state the proportion of women who initiated AZT by trimester, deleting the subjective comment.
Modified as suggested, Lines 243-5.

10. In the PREGNANCY OUTCOMES and BIRTH ANTHROPOMETRICS portion of the RESULTS section, beginning at line 250 on page 13, it is indicated that HIV-positive women experienced
higher proportions of adverse birth outcomes, followed by proportions of 41% and 31%. Please add a p-value so the reader can discern if these values are significantly different.

**Modified as suggested; Line 251.**

11. In the INFANT GROWTH portion of the RESULTS section, beginning on line 270 on page 14, it is stated that HIV-exposed infants “fared worse” with both underweight and stunting disproportionally affecting them “throughout infancy”. “Fared worse” is a subject term. Please omit and state that facts. Also, your cohort was not followed throughout infancy, which would indicate 12 months of life. Please clarify.

*We have changed this sentence to read: “HIV-exposed infants were disproportionally affected by underweight and stunting throughout the first 6 months” (Lines 269-71).*

12. In the INFANT GROWTH portion of the RESULTS section, beginning at line 274 on page 14, it is mentioned that infant growth differences based on HIV-exposure persisted, despite HIV-positive women reporting “better infant feeding practices”. While it is true that the period of exclusive breast feeding was longer, this length is still well below what is recommended by WHO. Of note, if you look at your graphics on WAZ and LAZ by maternal HIV status, there was a decline in both WAZ and LAZ from 1 month to 2 months for HIV-exposed infants, the period during which exclusive breastfeeding was discontinued. Please merely state that this difference was noted despite that fact that HIV-positive women reported a longer mean period of exclusively breast feeding. You can present the means after this statement and allow the reader to draw the conclusion of whether this represents optimal feeding of an infant.

**Modified as suggested, Line 274.**

13. In the INFANT GROWTH portion of the RESULTS section, at line 281 and 283, subjective terms of “Interestingly” and “Not surprisingly”. Please remove these from the RESULTS section. If you find the results interesting or are not surprised by the results, this should be commented on in the DISCUSSION section of the manuscript.

**Modified as suggested, Lines 281-3.**

14. In the INFANT GROWTH section of the RESULTS, beginning at line 288 it is stated that MUAC modeled as a continuous variable was significantly associated with overall infant WAZ and an effect estimate and p-value are provided. It may help the reader to actually state that in the multivariate model each 1 cm increase in maternal gestational MUAC was associated with a WAZ increase of 0.11, after adjusting for other maternal and infant characteristics (Refer to table 5).

**Modified as suggested, Lines 289-90.**

15. In the DISCUSSION section starting at line 301, it is stated that HIV-exposed infants were at greater risk of “poorer outcomes” in this study, despite earlier antenatal care and comparatively better infant feeding practices”. It is important for the word “growth” to be inserted between “poorer” and “outcomes”, as this study only looked at growth and not any other outcomes such as morbidity or mortality. Secondly, while I understand that, by mean duration of breastfeeding, HIV-infants had a “feeding advantage”, to allude to better infant
feeding practices is inappropriate as neither group of infants had an adequate length of exclusive breastfeeding.

Modified to include the word “growth”, Line 302. The observation that breastfeeding duration of both groups was far shorter than WHO recommendations is noted in Lines 367-8.

16. In the DISCUSSION section starting at line 304 on page 15, it is stated that poorer growth patterns among HIV-infected children are well-documented, however, two earlier reviews of African studies suggested that postnatal growth differences in HIV-exposed but uninfected infants were small or transient in early infancy compared to early to HIV-unexposed children. First, please do further literature search, as there a studies that have found differences in birthweight and growth in infancy, with HIV-exposed infants having poorer growth outcomes compared with HIV-unexposed infants.

Secondly, the authors have mischaracterized Suzanne Filteau’s paper which includes details on a cohort in the Democratic Republic of Congo where lower LAZ in the first half of infancy was noted among HIV-exposed uninfected infants when compared with HIV-unexposed infants. It also cites a Rwanda study which found statistically lower length through most of infancy and lower weight at six months of life. These results support your study’s findings. Please clarify in the manuscript.

We have modified this section of the manuscript. We have removed the sentence, “It is notable that these studies were conducted in urban African centers, and may not accurately reflect non-urban populations that experience numerous different health and health care access challenges” and modified the previous sentence to read: “Poorer growth patterns among HIV-infected children are well-documented and several studies have observed differences in growth outcomes between HIV-exposed, uninfected and HIV-unexposed infants in sub-Saharan Africa [17, 18]; however, there is also evidence suggesting that postnatal growth is similar between HIV-exposed, uninfected and HIV-uninfected children, or that differences between groups are small and transient [19, 20]”, Lines 305-9. Additional citations included.

17. In the DISCUSSION section starting at line 311 on page 15, a Malawian study involving HIV-infected women is summarized. It is stated that MUAC measured during pregnancy was associated with birth weight, while higher maternal MUAC was associated with lower likelihood of LBW. It may be more accurate to state that “MUAC measured at the study enrollment in pregnancy was positively associated with birth weight, and the risk of experiencing a LBW delivery decreased significantly with increasing maternal gestational MUAC.

Modified as suggested, Lines 310-3.

18. In the DISCUSSION section starting at line 313 on page 16, a study from Dar es Salaam is cited and it is stated that MUAC measured during pregnancy and analyzed in quartiles was associated with birth weight. However, the authors of this study actually only compared women with the highest MUAC quartile to those with the lowest quartile and found that women in with the highest quartile MUAC values gave birth to infants with higher mean birthweights. Please properly characterize this study.

Modified to read: “women with MUAC values in the highest quartile gave birth to infants with
higher mean birthweights compared to women with MUAC in the lowest quartile”, Lines 314-5.

19. In the DISCUSSION section, a large Tanzanian study is cited and it is mentioned that maternal gestational MUACs < 22 were more prevalent among HIV-infected ART-naïve women. While you rightly cite in the next sentences that this was in the pre-ART era, and so direct comparisons cannot be made, it is deceptive to point out ART-naïve status since 100% of the HIV-infected women in Wafaie Fawzi’s study were ART-naïve. I would strongly recommend that this come out of the DISCUSSION SECTION, or at least “ART-naïve” be removed.
Modified slightly, but still reflecting our interpretation of the findings of this cited study and the historical data.

20. In the DISCUSSION in the paragraph beginning on line 344, much focus is placed the fact that HIV-exposed infants have poorer growth outcomes and it is repeatedly emphasized that this is occurring in a rural and peri-rural setting. This finding is not unique to rural or per-rural settings. The study does not “contribute evidence that maternal HIV status is a risk factor for shorter birth length in rural and semi-rural Tanzania”. The message should be that we know from numerous studies that HIV-exposed infants have poorer growth outcomes compared with HIV-unexposed infants. Since the health of a child is driven by the first 1,000 days of life, from conception to the child’s second birthday, HIV-infected women require optimization of nutrition prior to conception and throughout pregnancy and their HIV-uninfected infants need to be followed closely to optimize their growth. We need interventions that can truly improve maternal nutritional status and optimize infant growth. This is not unique to urban or rural settings.
The phrase “rural and semi-rural” has been removed.

21. On line 392 in the CONCLUSIONS section, it is stated that maternal health did not differ according to maternal health status. It would be more appropriate to state that the prevalence of anemia and mean BMI of women participating in the study did not differ significantly by maternal HIV status.
Sentence modified to: “Maternal health based on standard clinical (e.g. Hb concentration) and gestational anthropometric indicators did not differ according to maternal HIV status…”, Lines 398-400.

Minor Recommendations:
1. In the RESULTS AND DISCUSSION section of the ABSTRACT, please clarify that the association between HIV-exposure and growth outcomes from birth to 6 months was as a result of multivariate regression, as the current sentence does not explain that these are adjusted effect modification values.
Added “multivariate”, Line 42.

2. In the METHODS section on page 8 starting at line 145, it indicates that women with a CD4+ cell count < 350 cells/µL were eligible for triple antiretroviral treatment. However, if WHO guidelines were being followed in Tanzania, than it should actually read “# 350 cells/µL or WHO clinical stage 3 or 4 irrespective of CD4 cell count”. Please change to “#” and add the clinical
stage criteria, if Tanzania was following these WHO guidelines at the time of the study. We have modified the text to read: “...CD4 cell counts ≤350 cells/µL or WHO clinical stage 3 or 4 irrespective of CD4 cell count were eligible...”, Lines 146-7.

3. In the METHODS section at line 196 on page 10, it is indicated that Student’s t-test was employed for normally distributed continuous variables followed by “or” ANOVA used for comparison of means across categorical variables. I believe it would be more grammatically appropriate to replace “or” with “and” and say that “analysis of variance (ANOVA) was used for...”. Corrected as suggested, Lines 197-8.

4. In the MEHTODS section on line 202 of page 10, it states that linear regression models were adjusted for gender. The correct term is sex. Modified as suggested, Line 203.

5. In the PREGNANCY OUTCOMES AND BIRTH ANTHROPOMETRICS section beginning on line 257 on page 13, reference is made to the fact that maternal HIV-seropositivity was associated with lower birth weight and length. However, these are mean values. The word “mean” needs to be inserted before both birth weight and length. Modified as suggested, Line 257.

6. In the PREGNANCY OUTCOMES AND BIRTH ANTHROPOMETRICS section, beginning on line 264 on page 13, interaction p-values are presented. For grouping purposes, it may be better to present gestational age at delivery first, followed by the four birth anthropometric measures. Modified as suggested, Line 264.

7. In the PREGNANCY OUTCOMES AND BIRTH ANTHROPOMETRIC section, beginning on line 269 on page 14, it is noted that 57% of infants were stunted at 6 months. Please include the number of infants that were stunted at six months. Modified as suggested, Line 269.

8. In the INFANT GROWTH section of the RESULTS, beginning at line 290 on page 15, please clarify that the findings with respect to infant HIV-exposure status were detected in the mixed effects model. Added “…in mixed effect models”, Line 292.

9. In the INFANT GROWTH section of the RESULTS, beginning at line 292 on page 15, it is stated that interactions were examined between HIV and gestational MUAC in these growth models. Please clarify. Does HIV refer to maternal HIV-status or infant exposure status? Added “maternal” before “HIV” to clarify in Line 293.

10. In the DISCUSSION section beginning on line 299 of page 15, reference is made to “nutritional risk”. It may be better termed as “nutritional status”. Modified as suggested, Line 300.

11. In the DISCUSSION section beginning on line 303 of page 15, reference is made that uninfected infants “continue” to have poorer birth and growth outcomes in this rural and semi-rural setting. Can you please clarify the term “continue”? I am not certain it adds any value or
accurately reflects the findings, as there is no prior report from this area of this same finding, is there?

We have modified this sentence by removing the word “continue”, Line 304.

12. In the DISCUSSION section starting on line 321 of page 16, reference is made to the strong and urgent call for POCT from resource restricted areas. Please provide citations. Furthermore, the characteristics of an ideal POCT are stated in the next sentences. Please provide citations for these requirements.

Citations have been added. For additional clarification, the sentence listing the characteristics of an ideal POCT has also been modified to say the following: “The ideal POCT has been described according to the ASSURED criteria (developed at the 2003 WHO Special Programme for Research and Training in Tropical Diseases) as being affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free (or requiring minimal equipment), and deliverable”, Lines 324-7.

13. In the DISCUSSION section starting on line 330 of page 16, discussion takes place about MUAC cutoffs in supplementary feeding programs. Please provide citations.

The appropriate citation has been added, Line 335.