Reviewer's report

Title: Gestational mid-upper arm circumference and birth or early infancy anthropometrics in HIV-exposed and unexposed infants: a prospective cohort

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Reviewer: Kathleen Powis

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Summary: In resource-limited setting with generalized HIV-epidemics, children born to HIV-infected women face higher morbidity and mortality. Many studies have reported that lower birth weight and length of HIV-exposed infants has been associated with increased infant morbidity and mortality. From this, it is clear that some component of the poorer infant health outcomes stems from events occurring in pregnancy. UNICEF has identified the first 1000 days of life, from conception through a child’s second birthday, as the most critical time period to optimize health and growth outcomes. Wilkinson and colleagues offer important findings on a well-established tool, measurement of mid-upper arm circumference (MUAC) among the women enrolled in their cohort to assess pregnancy outcomes and infant birth and longitudinal growth outcomes. Their linear regression models include maternal HIV-status as an independent variable. While their work will be of great interest to BMC readers working on optimizing pregnancy outcomes and the health of HIV-exposed and unexposed infants in resource limited settings, the manuscript could be improved upon in several areas. Presented below are recommendations for major and minor modifications.

Major Recommendations:

1. In the BACKGROUND section of the ABSTRACT, the authors indicate that rural populations represent an understudied group. While they likely represent a group with poor access to a sound health care infrastructure, there are numerous citable studies of pregnancy outcomes and maternal nutritional status in rural settings within developing countries. This needs to be either re-characterized to reflect the often limited healthcare infrastructure found in rural settings, multiple citations that substantiate the assertion need to be provided or the suggested research disparity needs to be removed all together. Of note, often the INTRODUCTION of a manuscript will echo key comments made in the BACKGROUND section of a manuscript. There is no reference to rural areas being “understudied” in the INTRODUCTION. Please correct this reference in the DISCUSSION section of the manuscript (lines 246 and 305).

2. In the METHODS section of the ABSTRACT it is stated that “Mid-gestation” anthropometry was obtained. However there is no definition of “mid-gestation” in the manuscript. Table 1 indicates that women were enrolled as early as 16.6 weeks gestation and as late as 34.9 weeks gestational age. It may be more
appropriate to define the timing of maternal anthropometric measurements as
either within the 2nd or 3rd trimester or specifically define the minimum and
maximum gestational age at which maternal anthropometry was obtained.

3. In the RESULTS AND DISCUSSION section of the ABSTRACT, the opening
line indicates that “gestational mid-upper arm circumference and HIV status
(HIV-positive=39%) were prognostic determinants of infant weight-for-age and
length-for-age z-scores from birth to 6 months, even after adjustment for infant
feeding practices”. First, this is a prospective observational study. Therefore,
causation cannot be established, but an association was found. Secondly,
“HIV-status” should be modified to indicate “maternal HIV-status”. While the
prevalence that follows implies a maternal HIV status and the methods section
will provide the reader with the fact that HIV-infected infants were excluded, the
abstract should be clear on its face without the reader needing to delve farther
into the manuscript. Lastly, reference is made here and throughout the paper to
“gestational mid-upper arm circumference”. Other literature on this topic refers to
“maternal mid-upper arm circumference”. This may be a term better understood
by readers.

4. In the RESULTS and DISCUSSION section of the ABSTRACT, it is indicated
that gestational mid-upper arm circumference was significantly associated with
“overall” infant weight-for-age and length-for-age z-scores, with respective effect
estimates of +0.11 for both outcomes. This finding needs to clarify that in linear
mixed effected models for WAZ and LAZ from birth through 6 months of life, each
1 cm increase in maternal MUAC was associated with +0.11 increased infant
WAZ and LAZ.

5. In the CONCLUSIONS section of the ABSTRACT, it is stated that “In rural
settings, HIV-exposure is associated with poorer anthropometry and growth
faltering throughout the first 6 months, despite improving antiretroviral access
and better infant feeding practices. It would be more factual to state that “In our
rural and peri-rural setting”, as not all rural settings have improved antiretroviral
access and better infant feeding practices. Secondly, reference to growth
faltering is made in this statement but the term is not defined in the METHODS,
RESULTS or CONCLUSIONS sections of the manuscript. Unless this is
expanded upon, this subjective term should be eliminated from the abstract.

6. In the BACKGROUND section, the final paragraph talks about use of maternal
MUAC in humanitarian crises settings and states that it is rarely used in antenatal
settings. You may want to refer to:


Of note, it may be particularly important to highlight that although maternal
MUAC has been reported in the past relative to birth outcomes, no reference
ranges exist.

7. In the METHODS section at line 100 it indicates that study eligibility included
gestational age of < 34 weeks. However, in table 1, the standard deviation of
maternal gestational age at enrollment indicates that some HIV-infected women were enrolled at least as late as 34.9 weeks. Please clarify the enrollment criteria.

8. The final sentence in the STUDY POPULATION portion of the METHODS section indicates that all infants remained HIV-negative. It is somewhat surprising that all infants were able to leave their rural or semi-rural setting, present to a regional hospital and have their PCR results returned to them in a timely manner. This would not be in keeping with the normal fall-out in the cascade of care of HIV-exposed uninfected infants and is somewhat surprising, as not all mothers were on triple antiretrovirals. Can you please confirm that definitive results were available on 44 infants at 3 months of life and non-breastfed beyond 3 months of life?

9. In the DATA COLLECTION portion of the METHODS section or the RESULTS section, please provide the percentage of gestational ages that required estimation of fundal height due to the fact that the mother could not provide an LMP.

10. In the DATA COLLECTION portion of the METHODS section, the scoring system for infant feeding practices is presented. However, further definition is needed around “1=partial breastfeeding” and “2=predominant breastfeeding”. Secondly, please clarify, since this score was developed to compare infant feeding practices at each visit, if an infant could receive a score of 2 at the one month visit and a score of 3 at the two month visit, as an example or was a score assigned once to the first six months of life. Just to clarify, an infant who exclusively breastfed through six month of life would have had a score of 12, or 3 at each of the 4 study visits after birth?

11. In the STATISTICAL ANALYSIS portion of the METHODS section, it states that infant anthropometrics at birth and gestational clinical characteristics were analyzed using simple linear regression, adjusted for maternal HIV status, age, parity, education, gestational age at the time of anthropometric measurement and infant gender. However, in reviewing Table 2 and 3, it appears as if univariate linear regression was performed as a first step followed by multivariate linear regression. This should be clarified in the METHODS section.

12. In the STATISTICAL ANALYSIS portion of the METHODS section, MUAC tertiles and maternal gestational MUAC as low or high are discussed. Please clarify that for MUAC tertiles, cut-offs were based on MUAC findings of the cohort and that for the dichotomous variable of low or high gestational MUAC, the midpoint of MUACs in the cohort was selected. It would also be helpful to clarify the exact tertiles and the dichotomous breakpoint in results section. Of note, the results section references low vs high MUAC tertile comparisons. So if this is not a dichotomous cut, it really needs to be better explained in the METHODS section.

13. In the STATISTICAL ANALYSIS portion of the METHODS section, reference was made to adjustment of the mixed effects models for potential confounding
variables. However, the approach, whether a priori inclusion of potential confounders or reliance of a p-value in excess of 0.05 to reintroduce a covariate into the mixed effects model is not described. Please clarify the approach.

14. In the MATERNAL CHARACTERISTICS portion of the RESULTS section, it is indicated that HIV-positive women enrolled significantly earlier in pregnancy. However, Table 1 indicates that they enrolled significantly later. Is the error in the text or in table 1? Also, in the DISCUSSION section on page 13, at line 250, it indicates that HIV-exposed pregnancies received earlier antenatal care. However, this is not portrayed as such in Table 1.

15. In the MATERNAL CHARACTERISTICS portion of the RESULTS section, the text reads that HIV-positive women were not significantly different from HIV-negative women in their health according to anthropometric indicators. How does anthropometric measures dictate health? Were they equally likely to be hypertensive, anemic or have TB based on comparable anthropometric measures? It does not appear that health data was collected in order for this statement to be made. Any adjustments made to this wording should also be applied to the final sentence of the manuscript, which makes the same assertion.

16. In the MATERNAL CHARACTERISTICS portion of the RESULTS section there is discussion of “ART”. It is not clear whether “ART” references both AZT monotherapy and triple therapy. Given findings that triple antiretrovirals taken in pregnancy result in decreased birth weight and are associated with lower longitudinal length-for-age z-scores, it is very important not to lump AZT-monotherapy and triple ARVs into a common category.

17. In the PREGNANCY OUTCOMES and BIRTH ANTHROPOMETRICS portion of the RESULTS section, it is stated that suboptimal pregnancy outcomes were common with 5% of pregnancies ending in stillbirth or miscarriage. It would be more appropriate to simply report the proportions without subjective characterization of the proportions. If these proportions are “common”, either relative to rates in Tanzania or globally, it would be more appropriate to make this connection with appropriate citations in the DISCUSSION section of the manuscript.

18. There is reference to prematurity in the manuscript. The more appropriate term is “preterm delivery”. An infant can be born on or after 37 weeks gestational age, yet have a physical exam that is consistent with prematurity. Please correct this terminology.

19. In the PREGNANCY OUTCOMES and BIRTH ANTHROPOMETRICS portion of the RESULTS section, it is reported that HIV-positive mothers delivered small babies and it then goes on to report “birth weight” as -235 grams. This is not a birth weight, but rather the expected difference in birth weight compared to an infant born to an HIV-uninfected mother. Furthermore, this is only in univariate analysis. In multivariate analysis the difference in birth weight indicates that infants born to HIV-infected mothers would be expected to weigh 281 grams lighter, after adjusting for other covariates. This is the result that should be
reported. It is not clear that the univariate model/results are needed.

20. In the PREGNANCY OUTCOMES and BIRTH ANTHROPOMETRICS portion of the RESULTS section, there is reference made to a dose-response relationship between MUAC tertile and birth length. This is not dose-response, but rather a positive association with increased birth length noted at each higher maternal MUAC tertile.

21. In the INFANT GROWTH portion of the RESULTS sections, several references are made to “strong associations”. It would be more appropriate to characterize these as “was found to be statistically significantly associated with...”.

22. In the DISCUSSION section starting at line 251, it is indicated that evidence from this study demonstrate that HIV-exposed pregnancies and infants continue to have poorer prognosis than HIV-unexposed infants in terms of birth and growth outcomes in this rural setting, despite improving antenatal HIV-testing, maternal ART and PMTCT implementation. There is no indication in this paper that HIV-infected women either conceived on triple ARV regimens or were started in the 14th week of gestation to indicate that this cohort had optimal PMTCT treatment. It is reasonable to point out the worse outcomes experienced by HIV-exposed infants, but not to target it to better PMTCT practices in this cohort. As a minor point, reference to HIV-exposed uninfected infant is probably a better overall description than HIV-exposed pregnancies and infants.

23. In the DISCUSSION section starting at line 288 it indicates that while maternal HIV care continues to improve and important reductions in maternal HIV transmission have been achieved in Africa, the findings of this study suggest that HIV-exposed pregnancies and infants living in this rural and semi-rural setting still have a poorer growth outcomes compared to HIV-unexposed infants. This comment fails to take into account the contribution of the ARVs to which a portion of the infants were exposed in utero. Studies have found that triple ARVs compared with mono-therapy are associated with significantly lower infant birth weight and longitudinal LAZ. Therefore, in this section, it would be more appropriate to acknowledge that while in this cohort, models were structured to compare maternal HIV-status, they were not able to isolate the impact of in utero exposure to ARVs.

24. On line 297 of the DISCUSSION section, it indicates that the study data extends further by demonstrating that maternal HIV status was a risk factor for short birth length. This is not a new finding and has been cited in the literature from sub Saharan Africa.

25. In the DISCUSSION section on line 303, it indicates that HIV-positive mothers exclusively breastfed for a significantly longer duration than HIV-negative mothers. While there was a statistically significant finding, the fact that HIV-uninfected mothers only exclusively breastfed for a mean of 3.4 weeks and HIV-infected mothers only exclusively breastfed for a mean of 6.6 weeks, it is well below WHO recommendations and breastfeeding practices in sub
Saharan Africa and both would be expected to impact growth. Given this very short window of exclusive breastfeeding, it would be important to provide the reader with mean weeks of exclusive breastfeeding, as well as mean weeks to breastfeeding cessation in the RESULTS section of the paper. Additionally, it should be pointed out in the limitations paragraph, that findings may not be generalizable to other settings, particularly rural settings in sub-Saharan Africa, where EBF is generally sustained for longer periods that approach six months of life, particularly in infants of HIV-uninfected women.

26. In the DISCUSSION section the reader is provided, for the first time, with the fact that complete birth anthropometric data was unattainable within the 72 hour period after delivery for 24% of the infants, a large number. This needs to be reported in the results and also needs to be reported by maternal HIV status. It cannot be discerned from Table 1 whether both exposure groups were affected by missing data.

27. In the CONCLUSION section, it opens by stating that “infant size is an important risk factor for early infancy morbidity and mortality in Africa”. I do not believe you will find a citation to report “size” as being associated with morbidity and mortality, rather lower birth weight has repeatedly been shown to be associated with increased morbidity and mortality. If you can find a “size” reference, please add it. Otherwise, please change to birth weight and provide citations.

28. In the DISCUSSION section, please clarify the clinical significance of the decreased birth weight and growth observed in this study. If these infants survived through six months of life, is this a clinically significant difference?

29. On Table 1, CD4 cell count is listed under the OVERALL column with a report of n=114. Yet the table footnotes are clear that this data is only for HIV-infected women. All data should be reported under HIV-infected women, without data in the OVERALL column. Also, the 3rd footnote is presented in the data table before the second footnote. Numbering and the legend below the table should be presented in order.

30. Tables 2 and 3 are very challenging to follow. First, it may help the readers to present this data in landscape format, so that all columns have equal width and the 95% CIs appear on the same line. This would also allow all negative effect estimates to appear beside their numerical value. For example, if the reader scans table 3, they might assume the HIV-infected women might give birth to infants weighing 280.38 grams more than HIV-uninfected women. Secondly, in the section of MUAC tertiles, please add the ranges for each tertile for the reader’s benefit. Finally, with respect to the letter designated footnote of significant differences in the between group comparisons, I am unable to discern how to interpret “a” versus “ab” versus “b”. Can this be clarified?

31. On Table 4, the prevalence of “WASTING” for HIV-exposed infants actually appears to be the prevalence of underweight (weight-for-age z-score of greater than 2 standard deviations below the norm of the reference population). If you
look across the time periods, WAZ is not declining at the same rate as LAZ. Since wasting is a function of weight-for-length, if weight doesn’t decline at the same rate as length, the infant’s weight is becoming increasingly more proportional to length over time, indicating that while incidence of stunting may be increasing over time, wasting would be decreasing. Please check this for the entire table.

32. For Table 4, please provide the ranges for “low gestational MUAC” and “high gestational MUAC”.

33. In Table 5, it would indicate that each additional week of exclusive breastfeeding was associated with a decline in both WAZ and LAZ of 0.02. Intuitively, this does not make sense. Is the variable coded correctly in the model?

Minor Recommendations:
1. In the CONCLUSION section of the ABSTRACT, reference is made to maternal mid-upper arm circumference being associated with “suboptimal” birth and infant anthropometry. The findings actually demonstrate that lower maternal MUAC is associated with lower birth and infant anthropometry. This is a more factual statement of the findings. The conclusion could incorporate the fact that this may place infants born to women with lower MUAC at greater risk for morbidity and mortality.

2. The CONCLUSIONS section of the abstract concludes with the statement “Gestational mid-upper arm circumference has the potential to identify at-risk women in need of additionally health invention that may prevent negative fetal and infant consequences. You may want to consider revising this to read “Routine assessment of maternal mid-upper arm circumference has the potential to identify at-risk women in need of additional health interventions designed to optimize pregnancy outcomes and infant growth.”

3. The final sentence of the CONCLUSIONS section of the ABSTRACT calls for further research to establish gestational mid-upper arm circumference reference ranges. It may also be appropriate to define a package of interventions that successfully improve MUAC in pregnancy.

4. In the second paragraph of the BACKGROUND section at line 70, there is a sentence which currently reads “While these indicators identify severe problems, they pregnant women with mild or moderate malnutrition may be unidentified”. Should the “they” be removed from this sentence?

5. In the final sentence of the second paragraph of the BACKGROUND section at line 75, it reads “…pregnancies that represent the crucial first step towards achieving better maternal, fetal and infant care…”. Should the “that” be removed from this sentence?

6. In the STUDY POPULATION portion of the METHODS section at line 104 it is indicated that women were followed from “mid-gestation” through delivery. Given
the comment above about the nebulous nature of “mid-gestation and that fact
that some women were only followed from 34 weeks through gestational, might it
be better to indicate that women were followed from time of enrollment through
delivery?

7. There appears to be a typo at line 192 on page 10 in the MATERNAL
CHARACTERISTICS portion of the RESULTS section where is states “or 3 triple
therapy”. Should this simply be “triple therapy”?

8. The word “women” is likely missing from line 194 on page 10 in the
MATERNAL CHARACTERISTICS portion of the RESULTS section, which
current reads “Among who began ART during pregnancy….”.

9. In the INFANT GROWTH portion of the RESULTS section, reference is made
to a rural cohort (line 220). This is actually a rural and semi-rural cohort.

10. In the INFANT GROWTH portion of the RESULTS section, there is likely a
typo at lines 229 where it reads “…tertile associated with significantly lower WAZ
at throughout infancy…”. The “at” should likely be deleted.

11. In the DISCUSSION section at line 283, these women probably need multiple
interventions, so intervention should be changed to interventions and “is”
following the word consequences should be changed to “are” to achieve
appropriate grammar.

12. It is redundant to say in the DISCUSSION section starting at line 286
“implementing the most appropriate maternal intervention for these women”, and
might be better worded as “implementing the most appropriate interventions for
these women”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.