Author’s response to reviews

Title: Growth, immune and viral responses in HIV infected African children receiving highly active antiretroviral therapy: a prospective cohort study

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Author’s response to reviews: see over
Melissa Norton MD  
Editor-in Chief  
BMC Pediatrics  

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Dear Dr. Norton,  

Re: Response to reviewers, Manuscript Title: Growth, immune and viral responses in HIV infected African children receiving highly active antiretroviral therapy: a prospective cohort study. MS: 749393037133912  

We thank both reviewers for reviewing our manuscript and giving us an opportunity to respond to their comments. We have responded to their comments in the order in which they were raised.

1st Reviewer: Prof. Sharon Nachman  

1. Unfortunately this study used WHO criteria for initiation of HAART based on 2003 criteria. Perhaps if more recent criteria were used we would have seen different growth parameters in those who were not the sickest of the children. Of interest, their finding of best success with children with CD4%>10% allows us to think that everyone would benefit from HAART.  

Response: In reference to use of the 2003 ART guidelines, the study was initiated in 2004, and the 2003 ART guidelines were the current guidelines at the time. However, during the study period (2004 – 2007) when the WHO ART guidelines were updated, we did not change the study entry criteria in order to avoid having children with different WHO and immune stages at study entry.

2. I suspect that stunting and underweight findings in Ugandan children and subsequent treatment with HAART for HIV may not result in all children attaining standardized growth. Factors including malnutrition in the household, infectious syndrome and other reasons for stunting will still be present, even after HAART therapy is initiated.  

Response: Thank you for raising these different factors that contribute to growth in HIV infected Ugandan children on HAART. We have added to the discussion…… “In the larger Ugandan population similar robust growth responses may not occur in all children initiating HAART because of varying infectious diseases and socio-economic factors in the home”. (Pg 14 paragraph 2 – last sentence)  

3. In the future it will be critical to monitor adherence, development of resistance and long term toxicities of these therapies if the growth gains noted here are to be continued.  

Response: Thank you for these comments. We have incorporated them into our discussion.
2nd Reviewer: Prof. Celia DC Christie-Samuels

1. The methods to accomplish these objectives seem appropriate and are well described. However, the weakness is that an appropriate comparative control group, such as, age-matched, HIV-exposed children but HIV-negative children from the same communities were not included. On page 12, first para of the discussion, the authors make a strong case for increased growth velocity in younger children as compared to older children (which is expected) and without an appropriate control group, I wonder if these conclusions should be worded so strongly.

Response: We will include this as one of our limitations since the study design was only to follow HIV infected children who initiated HAART and there was no control group to compare with. The strength of the wording will be toned down to say (Pg 12 1st paragraph) ...... “The younger VF/IS group experienced a robust growth response despite failing to completely suppress virus on therapy.” (Will exclude comparison to the older children)

2. The data are sound. However, is clarification needed for subject accounting, viz?
Page 5: 130 HIV-infected children were enrolled…. 124 had growth measurements available and completed followup …. except 7 who died (should leave 123, yes?)

Response: Thank you for pointing this out. We will make the necessary clarifications in the text. Pg 5, There were 130 children enrolled and 7 died, giving a total of 123 children (correct) however one child died after 44 weeks of follow up so we had most of their growth, immune and virological data to that time point, when they were censored. Will add a sentence to clarify this so that the numbers add up ...
Pg 5, “For this analysis, 124 children had growth measurements available and 123 completed the 48 weeks of follow up. Seven children died during the study follow up but one child died after 44 weeks of follow up and therefore had data for almost all the study time points except for week 48.” Pg 5, 1st paragraph – last 2 sentences.

3. Page 9, para 1, Then “98% (122/124) completed followup”, contradicting the next sentence where it states that “Seven children died during study follow up”

Response: Pg 9, paragraph 1 -Thank you for pointing out this inconsistency. It will be corrected to read... “All the children were ART naïve at enrollment and 95% (123/130) completed 48 weeks of follow up.”. Pg 9, 1st paragraph – 2nd line.

4. Page 14, last para, then states that “no child lost to follow up”? Clarification

Pg 14, last paragraph. Thank you for highlighting this statement which is unclear. It is correct that no children were lost to follow up, “except for those who died”. Therefore these words will be added to the sentence to clarify this statement. Pg 15 – 4th line

5. The discussion and conclusions are well balanced and adequately supported by the data. However, more could be said throughout the manuscript about “other clinical factors” although WHO staging mentioned briefly, this was part of the stated objective.

Response: The other clinical data were not analyzed separately and we used the WHO criteria as a surrogate marker for clinical events. So, we have included a general comment about clinical events. We have added a general comment......... “After HAART initiation the children had
fewer sick visits during weeks 24 – 48 when compared to the initial 24 weeks on therapy (data not shown).” Pg 9, 1st paragraph- 7th line.

6. Page 13, second para, I wonder if some comments could be made about early infant diagnosis with DBS testing to identify infected infants by 4 months of age, to initiate HAART, even before they become symptomatic? Is it possible in this setting?

Response: We have added a sentence about the use of DBS to identify children early in infancy. Uganda is implementing an early infant diagnosis (EID) program using dried blood spots (DBS) but has limited national coverage. A reference for the DBS has also been added. (#29)


7. But for the lack of a control group, the limitations of the study are clearly stated.

Response: We have added the lack of a control group as a limitation on pg 14, third paragraph.

8. Pg 12, second para, first line: I wonder whether the statement could be expanded, viz: Similar to other studies from Africa and other parts of the developing world ….. and the relevant references added ?

Response: Thank you for this comment, we have added to the text ……..other resource limiting settings and the relevant references have been added. Pg 12, 1st sentence of discussion.

Additional references (# 23, # 24)


9. Minor Essential Revisions to Table 1

Response: Thank you very much for pointing out the inconsistencies in table 1. The percentages have been removed from the actual numbers and left in the subtitles and years has been added to the age variable.

We express our sincere gratitude to both reviewers for providing important comments and suggestions to improve the manuscript. I hope we have answered all the questions and made the necessary revisions to make the manuscript acceptable for publishing.

Sincerely,

Dr. Philippa Musoke
Associate Professor