Author's response to reviews

Title: Durability of Antiretroviral Therapy and Predictors of Virologic Failure Among Perinatally HIV-Infected Children in Tanzania: A Four-Year Follow-Up

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Version: 3
Date: 18 August 2014

Author's response to reviews: see over
We thank the reviewer for noting the importance and value of this research and for a helpful and thoughtful review. Please find our response to the reviewer’s comments below:

**Major Compulsory Revisions**

1. As it is currently organized there are many different issues raised with data presented from 2 different studies- this makes it somewhat hard to follow so tighter organization of the issues being raised would be helpful. There are several themes intertwined that could potentially be separated into 2 different papers: durability of currently used regimens and sequencing of peds 1st and 2nd line; value of routine VL testing in children and adolescents and increased risk of treatment failure in adolescents.

   a. We appreciate this feedback and realize there are several interesting results from this study. We feel, however, the primary research data available does not offer the substance required to create two independent manuscripts, thus we thus have followed the reviewers advice to create a “tighter organization” of the discussion. The themes mentioned are discussed in separate paragraphs of the study as follows: 1) Durability, first paragraph of the discussion (301); Sequencing (beginning line 371); 3) value of routine VL testing (new paragraph, beginning line 313); increased risk of treatment failure/poor adherence in adolescents (beginning 325).

2. The current manuscript does little to put this data into the context of the new recommendation for routine VL monitoring which is currently being scaled up in Tanzania

   a. We appreciate the suggestion to situate the discussion in the context of WHO guidelines with regard to viral load testing (new paragraph added for this purpose beginning line 313). As the guidelines state, these recommendations and the reality of implementation can be discordant depending on the capacity of the individual country. Currently our region of Tanzania continues to rely on immunologic and clinical criteria, though we are hopeful this will soon change as capacity is being built and laboratory equipment procured.

3. The difference in the number/% of identified failures between the 2 studies is striking as is the difference between the number of children switched as a result of findings from the 1st study v. the number of new switches to 2nd line in the intervening years before the 2nd study was conducted (If I am interpreting Table 2 correctly). It is not mentioned if targeted VL was available and clinicians were relying on clinical/immunological signs of treatment failure or were able to obtain VL for suspected failure. However the authors fail to comment on this- my sense is that this may be a combination of the fact that treatment failure may be more likely in earlier years of treatment but also the insensitivity of clinical/immunological criteria.

   a. You have indeed interpreted Table 2 correctly and we have further clarified the intermittent switches (Methods: line 176-179; Results: line 240-242). In the interim of the first and second study EGPAF and private funding supported VL intermittently which was ordered somewhat haphazardly. Though our data cannot elucidate the best schedule for routine VL testing, it is clear that evidence-based guidelines will be important to guide therapeutic monitoring.

4. In the discussion section it is suggested that ABC and TDF should be considered for first line treatment- however it should be mentioned that in new WHO guidelines they are both preferred 1st line NRTI’s for children 3-10 and >10 years respectively.
a. Thank you for pointing out this important point. We have now included this recommendation by WHO in our discussion, noting that Tanzania has not fully incorporated these guidelines into current practice (line 381-383).

**Minor Essential Revisions**

5. In the subtype and resistance mutations section the paragraph 272-277 could be clarified by switching the 2nd and 3rd sentence.
   
   a. We believe we have followed this suggestion and agree it reads more clearly with relation to Figure 2. Line numbers are a bit different in this version reflecting revisions.

6. 90-91 The number of new peds initiations has actually been on the decline lately and though it may not be the subject of this paper, it may be more accurate to just point out the increasing number of pediatric patients on treatment and surviving into adolescence
   
   a. We have reworded this sentence and agree with the reviewer comment (line 86-89).

**Discretionary Revisions**

7. The phase out of d4T and ddI are mentioned here but would be helpful to mention when this occurred
   
   a. Ddi phased out in 2012 (line 143); d4t still used in rare circumstance, but has been on the list to phase out since 2013 (line 225)

8. The data presented here potentially could suggest the need for an alternate schedule for VL monitoring that takes into account higher risk of poor adherence/treatment failure for adolescents.
   
   a. Though our data are not able to definitively determine the optimal testing schedule, we have further discussed the WHO recommendations and that our data do suggest that adolescents are a high risk population that may require more frequent then annual testing (line 320-323).

9. Has there been consideration of repeating RT? Particularly for patients failing 2nd line as the point is made that a significant % were failing on their current 2L and 3rd line is not yet available and other studies have suggested that failure on 2nd line is presumed to be due to poor adherence in most cases.
   
   a. Though failure is often due to poor adherence, the resistance profiles measured in this study and others suggest that accumulation of NNRTI resistance with the currently available options NVP and EFV would not favor re-introduction of this drug class due to resistance mutations. PI’s are much more potent, have a higher barrier to resistance, and if re-initiated by mal-adherent youth, they will often result in suppression. We chose not to add this topic into the paper at this time.

10. In addition to bone mineral and renal toxicity, another factor that would discourage consideration of TDF in younger children is the limited availability of an appropriate and affordable pediatric formulation (currently available formulations from the innovator company are significantly more expensive than available generic formulations of ABC)
   
   a. Thank you. This has been added/edited (line 383-387).