Reviewer’s report

Title: Adherence to Antiretroviral Therapy among HIV Infected Children in Mekelle, Ethiopia

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Reviewer: Rachel Vreeman

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'Adherence to Antiretroviral Therapy among HIV Infected Children in Mekelle, Ethiopia'

Pediatric ART adherence is a critical topic for consideration for the long-term care of children with HIV. This study offers a fairly basic evaluation of children’s adherence, using an unvalidated questionnaire and minimal evaluation of child-related factors; however, it may provide an adherence estimate for a setting where adherence is not otherwise well-described, which could be a valuable start.

Major Compulsory Revisions

1. The research question is reasonably well-defined in terms of evaluating the rates of adherence cross-sectionally although there are significant limitations to this one-time, single-method strategy of measuring adherence. The methods used in this study reflect methods commonly used for adherence measurement in resource-limited settings – a caregiver report of medication adherence. However, there are significant limitations to these measures, some of which may be helped with further clarification. Caregiver reports may be susceptible to desirability biases, a problem that can be enhanced by using child self-reports or other adherence measures. Furthermore, the cross-sectional nature of the study design limits the ability to comment at all on adherence over time. These limitations need to be addressed throughout the paper, with more care taken to explain the measurement methods, the reasons for choosing a particular method, and the strengths and limitations of that type of measure.

2. Throughout the paper, the authors need to use caution in their statements of how they found factors causing non-adherence. This study cannot show causation, but can only suggest some factors with significant associations.

3. The authors should describe who administered the adherence measurement questionnaire. Was it done by clinicians in the course of routine clinical care or was it done by separate research staff?

4. To assess these findings appropriately, we need more information on the questionnaire. Were the questionnaire item or items validated? How was validation done? If a measure validated in another setting was used, how did the investigators ensure cross-cultural adaptation besides translation? How were the reasons for non-adherence developed? Where did the response options come
from?

5. Were any comparison measures of adherence such as pill counts, electronic dose timing information, or any other strategies used? Is adherence routinely assessed in this setting during clinical care? If so, by what measures? And could those measures be compared with these questionnaire findings?

6. The sample size calculations need to be better justified to give me confidence in the Methods and analysis.

7. Data analyses could be described in more detail to add confidence that appropriate adjustments for confounders were made.

8. The study population needs to be described in more detail in order to assess whether the Methods are appropriate. What is the total number of HIV-infected children cared for in this setting? What percent are on ART? What regimens available? How many eligible children have access to ART? How long have the sites been offering ART?

- The other questionable feature of the Methods is the seeming lack of information about the child. The caregivers’ characteristics are discussed in more detail. Critical information about the children such as disease staging or evidence of immunologic status are not included. Please explain. How does adherence on this measure compare other child characteristics like CD4 or viral load?

9. The discussion would be improved by discussing these limitations to the Methods in greater detail.

10. In addition, the significant factors related to the caregiver could be explained more clearly. Why is that particular age group thought to have better adherence? Why are married and unmarried caregivers having better adherence?

11. For the discussion, the authors should consider that there are several studies discussing children’s adherence to ART elsewhere in East Africa that could be included for comparison. They should include references to some of the other East African pediatric ART adherence studies (Uganda, Kenya) that are not included. In addition, the following systematic review is likely of relevance, especially to evaluate the measurement considerations: Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A systematic review of pediatric adherence to antiretroviral therapy in low- and middle-income countries. The Pediatric Infectious Disease Journal. 2008 Aug;27(8):686-691

12. Throughout the discussion, authors need to use caution when describing their results. Causation was not proven and limitation of the sample size may be responsible for the lack of significant effect for many factors.

13. The limitations of this type of analysis need to be described in more detail in the Discussion section.

14. Discussion, Page 8: Cannot truly say study showed that provider-patient relationship is not significant. More accurately, this was not a factor significantly associated with adherence here. But you cannot make too strong a statement given the study design and what the study was powered to show. Also, how was this assessed? And was it included in multivariate analyses? It is tricky to measure relationship dynamics with this kind of study.
15. Several parts of the abstract should be clarified:

a. First line: The statement about pediatric adherence being more complex than adult should either be supported briefly with an explanation as to why it is more complex or else removed.

b. Should not refer to their objective as finding “determinant factors” for adherence rates. This is a study that can show a significant association, but not causal effects.

c. The abstract should make clear which are uni- or bivariate results and which are multivariate results.

d. It is confusing in this Results context to list “unmarried” and “married” as both being significant. What is the referent group?

e. Conclusion: “encouraging the fundamental role of caregivers.” You have not described what the fundamental role is.

Minor Essential Revisions
1. The writing would benefit from thorough editing and review for grammatical errors and corrections to the English.

2. 3rd paragraph of Introduction: The authors say there is a “direct relationship between viral failure risk and drugs missed”. They need to provide a reference for this statement.

3. Results: Need to make clear that you are reporting age of caregiver here, not age of child as is more usual for a pediatric population.

4. Not clear in beginning of results who is depressed – caregiver or child? How was this assessed? Was a validated measure of depression used?

5. Was there any measure of treatment interruptions? Delayed doses?

Discretionary Revisions
1. The title might be changed to “Caregiver-Reported Adherence…” to reflect the measure used.

2. Do not need to describe exact geographic location, temperatures, altitude for this setting.

3. Please consider creating a figure with the questionnaire items or putting the questionnaire in an appendix.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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.