Author’s response to reviews

Title: Adherence to antiretroviral therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers’ report

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Authors’ response to Reviewers’ comments

Adherence to antiretroviral therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers’ report

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Dear Editor,

First of all, we are grateful for the critical and thoughtful comments of the reviewers that improved our manuscript.

We have considered all the comments thoroughly and made all the necessary revisions in the manuscript (Please see the revised manuscript for the specific changes made). Besides, a point-by-point response to each comment has been provided (in blue) in this cover.

General response:
The manuscript has been checked for formatting and style. It has been edited and language errors were corrected.

Response to Reviewer #1: Mogomotsi Matshaba

Background:

Comment 1. Background paragraph 2, choice of word, replace curve with curb (DR)
Response: The word “curve” is replaced with “curb”

Materials and Methods

2. Study area: Well written paragraph but the backgrounds needs to be Clearer: Actual drug regimen available: first line, second line. The state of the supply chain management needs to be clear especially for pediatric formulations. Liquid formulations tend to be more difficult to administer and monitor. It is not clear if all were pills or liquids. Cultural issues and stigma could have been stated here as they all ultimately affect adherence. Routine labs followed can also be used to triangulate these data. (MER)
Response: More details have been included in this section as suggested (Materials and methods, study area, paragraph 2)

Study Design and study participants:

Comment 3. Timing: This is one of the busiest time in the Ethiopian calendar with several celebrations and festivities: Christmas Genna, January 7th, Timkat, Kullubi. It is well known
that during festive season, adherence becomes poor where stigma is still an issue. Impact
should be discussed. (DR)
Response: We acknowledge that the timing might have underestimated the level of adherence
and this was discussed as a limitation (Discussion, paragraph 8 lines 3-5)

Comment 4. Define the inclusion/exclusion criteria well, what was the lower age cut off.
(MER)
Response: Inclusion/ exclusion criteria were more clarified (materials and methods, study
design and study participants, line 5)

Methods of Data Collection
Comment 5. Timing of the laboratory data should be clarified, i.e. up 6 months prior to study
entry. (MER)
Response: Current CD4 count was the CD4 count recorded within 6 months of data collection
and this has now been included (Materials and methods, study area, paragraph, line 9)

Comment 6. Pill counts were conducted a week after interview, did the parents know that?
(MCR)
Response: Although parents were asked for a home-visit, they were not informed that pills
were to be counted until a home visited was made. Subsequently, during the home visit,
caregivers were asked for their consent for pill count. This was done to avoid information
bias and this has now been clarified (materials and methods, methods of data collection,
paragraph 1, line 7).

Operational Definitions
Comment 7. Period assessed for adherence was too short; will underestimate true adherence
especially for once daily dosed efavirenz. (DR)
Response: We acknowledge that this was a limitation; the reason we limited the time to 7
days is to minimize recall bias for caregivers’ report. Besides, if we take different time lengths
for the pill count and caregivers’ report, it would be difficult to compare the results. As rightly
commented, this might have underestimated the true level of adherence for efavirenz; we still
believe that this study has provided important information with regard adherence despite its
limitations.
Data management and analysis

Comment 8. Appropriate tests, Chi square tests and multivariate logistic regression were chosen for these data. See my comment on results below. (MCR)
Response: This has been addressed below in the results section (see response for comment 18, 21 and 22 below)

Ethics
Comment: Well covered

Results
Paragraph one: Socio Economic

Comment 9. Age breakdown of the children not very useful; we know adherence becomes a problem with teenagers. It is not clear how many are strictly supervised, just reminded or takes medications independently. (MER)
Response: According to the caregivers, all were strictly supervised; however, this may not be true for all children as most were in fact found to be non-adherent. There was no significant association between age and adherence in this study.

Social and Disclosure variable of children

Comment 10. Did not assess the child’s understanding of disclosure. It would be a much more objective way of assessing this important factor. (DR)
Response: Unfortunately, this was not possible in this study since most of the caregivers were not happy to have a discussion with their child. A qualitative study exploring this and other key issues might reveal important information on children’s understanding of disclosure.

Comment 11. Define what 4c/4d mean for the drug regimen. (MER)
Response: Definitions for each regimen has been included (Materials and methods, study area, paragraph 2, line 2)

Comment 12. Define what other regimens the rest of the patients were on. (MER)
Response: Second line regimens some children were taking are included in the manuscript (Materials and methods, study area, paragraph 2, line 5)
**Clinical Marker of children on ART**

**Comment 13.** Include mean time from initiation (DR)

*Response:* This has been included (since mean (47.8 months) and median (48.0 months) were close enough, median time with interquartile range was reported (Results, clinical markers of children on ART, paragraph 1, line 1)

**Comment 14.** Paragraph 1: It is difficult to compare pill counts to parent reports. Level of adherence is different i.e., for self report it is 100% meaning no missed doses while it is 95% for the home pill counts. (MER)

*Response:* We acknowledge that this was a confusing statement. Adherence was already defined under the operational definitions and this definition was used both for pill count and caregivers’ report. A child was adherent if he/she took at least 95% of the doses prescribed for one week. This has now been clearly indicated (Results, Adherence, paragraph 1, line 2).

**Comment 15.** Paragraph 2, could have compared those with extra pills vs. those without after correcting for other factors. (DR)

*Response:* This was compared if there was a difference among the two groups after correcting for other factors. There was no significant association between number of extra pills and adherence status (p=0.46). This has now been included (Adherence to ART, paragraph 3, line 3).

**Comment 16.** Paragraph 3 reason for children refusing medications and their ages would make this more useful information. Younger children might be taste or smell while older children reason might be pill fatigue, pill burden or stigma related. (DR)

*Response:* Unfortunately, data on reasons for refusing medication was not collected. As rightly commented, this would have given us valuable information.

**Comment 17.** Paragraph 4: I am not a statistician but seem to me that the logistic regression model was not interrogated fully. Some conclusions cannot be made with the information as presented. Variables need to be included and excluded multiple times or corrected for before some conclusion can be made. (MCR)

*Response:* Logistic regression has been repeated by an epidemiologist. After controlling for some selected variables, baseline CD4 count and duration of ART treatment lost statistical
significance. However, the other predictors of adherence remained statistically significant as before (Table 3).

Comment 18. Example one is not clear whether the marital status conclusion was based on other variables like age, educational level, income status factored in. Same applies to the disclosure conclusion, was age, sex, and level of disclosure corrected for? (MCR)
Response: We have now controlled for age and sex of child, caregivers’ age, caregivers’ sex, caregivers’ education and income. The association between adherence and disclosure of HIV sero-status as well as caregivers’ marital status remained statistically significant (Table 3).

Comment 19. Paragraph 5 given the short duration of assessment of adherence, one week, the difference in the denominator for calculating adherence become critical. One missed dose of EFV results in poorer adherence than one missed dose of NVP given that there are once daily and twice daily dosing respectively. (MCR)
Response: We acknowledge that this was a limitation; the reason we limited the time to 7 days is to minimize recall bias for caregivers’ report. Besides, if we take different time lengths for the pill count and caregivers’ report, it would be difficult to compare the results. As rightly commented, this might have underestimated true level of adherence for efavirenz; we still believe that this study has provided important information with regard adherence despite its limitations.

Discussion
Comment 20. Paragraph 2 line 3, change finding to findings-grammar (DR)
Response: This has now been corrected

Comment 21. Paragraph 4 see my comments on results above paragraph 4. It is not clear if age and other variables are included and corrected for in the model. If done this might actually be an age or experience factor rather than marital status. (MCR)
Response: we included variables suggested (see response to comment 18) and marital status remained significantly associated with adherence after controlling for caregivers’ age, sex, educational status and income. Better experience of those ever married than those never married in caring for children might be the possible explanation.
Comment 22. Paragraph 5: same argument as above. In other settings, controlled early disclosure leads to favorable outcomes. (MER)

Response: Here we included the aforementioned variables including age and sex of children and child’s awareness of his/her HIV status was significantly associated with poor adherence. This, as discussed in the manuscript, is a controversial issue. Some studies indicated that those children who were not aware of their sero-status were more adherent to their medication (references 19, 31, 32) and still others (reference 15 for example) reported that HIV sero-status disclosure is associated with good adherence. A difference in making children ready for disclosure as well as subsequent counseling to help them accept their status might account for the difference observed across settings.

Comment 23. Paragraph 6 see argument for results paragraph 5. This is not a fair comparison. (MER)

Response: This comparison has now been omitted

Comment 24. Paragraph 7 Weaknesses acknowledged well. Others include comparing different adherence monitoring modalities, recall bias, selection bias and the holiday season impact. (DR)

Response: These limitations have now been discussed (Discussion, paragraph 8)

Conclusion

Based on the results and discussion.

With more interrogation of the data, different conclusions may be drawn.

Overall Assessment

Comment 25. The results of the logistic regression need to be interrogated more rigorously by a statistician or epidemiologist. This study cannot be published until all major issues raised (MCR) are corrected. It is difficult at this point to firmly make most of these conclusions.

Response: The logistic regression analysis has been done by controlling other potential confounding variables and there are some changes in the results as described above (responses to comment 17, 18, and 21) and we believe we have now addressed the concerns raised.
Reviewer # 2: Bernadette O'Hare

Major compulsory revisions

Comment 1: Need to clarify between median adherence versus the percentage of children who achieved >95% adherence
Response: To avoid confusion, median adherence has been removed.

Comment 2: Need to clarify if the difference between the number of pills versus the number of Doses
Response: This has been corrected as the number of doses (Table 2 and adherence, paragraph 3)

Comment 3: Need to clarify if the pills already at home were counted
Response: The pills at home were counted but not included in calculating level of adherence. This has been further clarified in the manuscript (Methods of data collection, paragraph 1, line 12)

Comment 4: Need to stratify CD4 by age
Response: As rightly commented, age affects CD4 count. Analysis has been done after stratifying with age and there is a significant improvement in the CD4 count in all age groups. Since those children 5 years and younger were small, further categorization was not possible (Clinical markers of children on ART, paragraph 1, line 5).

Comment 5: There are three figures but stated that there are two figures
Response: It was a wrong duplication of figure 2. A correction has been made.

Detailed comments in attached manuscript

Additional comments in the manuscript:

Comment 6: was this interview after consent was it at routine outpatient clinic was it always 1 week after the interview that the home visit occurred? (Abstract, methods)
Response: This was more elaborated in the abstract (methods) as well as materials and methods section (methods of data collection, paragraph 1, line 5)
Comment 7: 93.3% of caregivers reported 100% adherence in the last week. In the results section you state that the median adherence on home based pill count was 89% and that 34.8% had adherence >95% - I think this could be stated a little more clearly to avoid confusing the reader

Response: This was clarified to avoid confusion as follows: for both pill count and caregivers’ report, adherence was operationally defined as taking at least 95% of the doses prescribed (materials and methods, operational definition) and this was followed. Accordingly, this has been corrected. The median adherence was removed since we thought it would result in confusion and may not add important information.

Comment 8: this could be influenced by the age as young children have higher CD4 counts, is this stratified (Abstract, results)

Response: stratifying by age did not have any influence either on the CD4 count improvement over time (please see response to comment 4 above) or on the logistic regression model in this study. However, upon controlling for age of caregivers, income, sex of caregivers, education of caregivers and age of child, baseline CD4 count was not associated with adherence and hence this has been corrected in the abstract, results as well as discussion section. Please see the response to comment 14 below as well.

Comment 9: is this for adults and children (Background, paragraph 1, line 3)

Response: yes, it is for both children and adults

Comment 10: was the interview done at a routine clinic appointment. Was the caregiver asked permission for the home visit? IF so may this have biased the results? (Materials and methods, method of data collection, paragraph 1, line 6)

Response: The interview was done at a routine clinic appointment and caregivers were asked permission for a home visit but were not informed regarding pill count until the home visit to avoid bias. This has been more elaborated (Materials and methods, method of data collection, paragraph 1, line 6).

Comment 11: were these pills which were left at home included in the subsequent pill count? If they were excluded then this needs to be stated

Response: this has been clarified (please see our response to comment 3 above)
Comment 12: why is being > 9 years important (Results: socio-demographic characteristics of caregivers and children, paragraph 1, line 4)
Response: Children usually start to question why they continue taking medication at around 9 years and this could be an opportunity to disclose their HIV sero-status if not already disclosed.

Comment 13: full names of drug regimens should be given the first time they are mentioned (Results, social and disclosure variables of children, paragraph 2, line 4)
Response: this has been corrected as suggested (study area, paragraph 2)

Comment 14: for this to be meaningful we would need to have it stratified by age and know the median length of time on ART (Results, under clinical markers of children on ART)
Response: Median duration has been included. On stratifying by age, the increment in CD4 levels remained statistically significant (p=0.005 (<5 year), p<0.001 (>5 years)). Those children 5 years and below were small (13 children) and further categorization was not possible (please see the response to comment 4 above).

Comment 15: The objective of the paper is to assess adherence - I would put this earlier in the results Adherence (Results, adherence)
Response: the reason we put this at the end of the results section is because we feel the sections prior to adherence are mainly background information relevant to the interpretation of the adherence results.

Comment 16: In the abstract it is stated that adherence was 34.8%. It would be useful to compare median adherence by report to the median adherence by pill count and also to compare the percentage of children who achieved 95% adherence by report to the percentage of children who achieved 95% adherence by pill count which you have said is 34.8% (Results, adherence, 2nd paragraph, line 1)
Response: This has been more clarified; however, the median adherence for caregivers’ report was not included since the vast majority (93.3%) of children were reported to be adherent to their treatment even when a 95% adherence rate was used to dichotomize as adherent and
non-adherent. The median adherence rate was 100% for caregivers’ report. Hence to avoid confusion, median adherence rates for both pill count and caregivers’ report were removed.

**Comment 17:** but this figure depends on the number of pills per dose - describe as the number of missed dose (Results, adherence, 3rd paragraph, line 1)

**Response:** this has been changed to doses (Table 2 and adherence, paragraph 3)

**Comment 18:** but this depends on the number of pills they had at baseline see line 28- need to state if the pills remaining at home were counted in this pill count (results, adherence, paragraph 3, line 3)

**Response:** extra pills left at home were counted but not included in the calculation of adherence rate. The pills remaining at home were counted separately to have insight on the number of extra pills they had until they received the last refill as well as to see if there was an association between the number of extradoses and level of adherence. There was no association between level of adherence and number of extradoses found at home (p=0.46).

**Comment 19:** but is disclosure not also influenced by age and may this not be a confounding factor? (Results, adherence, paragraph 6, line 3)

**Response:** It was controlled for age and the association remained significant (Table 3).

**Comment 20:** CD4 count varies by age and this would need to be stratified by age to be interpreted e.g. <2 yrs, 2-5 yrs and >5years (results, adherence, paragraph 6, line 4)

**Response:** Please see responses to comments 4, 8, 14 above

**Comment 21:** it was 89%, the figure 34.8% is the percentage who had achieved 95% adherence (discussion, paragraph 1, line 7)

**Response:** please see paragraph 1 above

**Comment 22:** did they define adherent as >95% (discussion, paragraph 1, line 11)

**Response:** Yes

**Comment 23:** you need to state what your study adds to those already done? It may be that it confirms others findings for Addis (discussion, paragraph 1, line 15)
Response: We believe this study added important information. Previous studies in Ethiopia used self-report method and reported a high level of adherence (which is the case in this study as well for caregivers’ report). However, caregivers’ report alone seems to be unreliable overestimating the level of adherence. In this study, pill count revealed a low level of adherence compared to caregivers’ report (Discussion, paragraph 1, line 1) implying that caregivers’ report alone is unreliable measure of adherence.

Comment 24: Did this study look at hospitalization rates? (Discussion, paragraph 7, line 5)
Response: this study didn’t look into hospitalization rates; however, the study cited has reported an association between good adherence and repeated hospitalizations; hospitalization indicates advanced disease and in our study we also found that those with advanced disease (Stage III and IV) were more adherent to treatment compared to those who have less advanced disease. This was the rationale for comparing our finding with the findings of the study cited.

Comment 25: The DART and ARROW studies would not support routine CD4 (conclusion paragraph 2, line 5)
Response: We do acknowledge that The DART and ARROW studies would not support routine CD4 count for clinical management of patients; however, measuring CD4 count and viral load is important to evaluate the correlation between level of adherence and clinical conditions of patients.

Comment 26: would it be possible to also give this in international currency (Table 1, monthly income of caregivers)
Response: This has been converted into international currency (Table 1)

Comment 27: this is repeated below (Table 1, child knows his/her sero-status)
Response: This has now been removed from Table 1

Comment 28: Should it not be the number of doses missed as the number of pills will depend on the weight of the child (Table 2, pills missed in one week)
Response: This has been corrected
Comment 29: I think this should be the number of doses (Table 2, extra pills at home)

Response: This has been corrected

Comment 30: What does ref mean (table 3)

Response: Ref was meant to be reference and this has been written in full

Comment 31: This needs to be age stratified or else just give the numbers for children >5 years as most of your children are aged > 5 years (Table 3, CD4 count)

Response: this has been clarified (please see our response to comments 4, 8, 14)

Comment 32: there is already figure 1

Response: this has been corrected (only figure 1 and 2 are included, the other deleted)