Author's response to reviews

Title: Adherence to Highly Active Antiretroviral Therapy and its correlates among HIV infected pediatric patients in Ethiopia.

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Author's response to reviews: see over
**Point by point response**

Dear reviewers:

We are pleased to have your critical comments. Please find point by point response to your comments.

**Reviewer:** Marcelo Soares

**Major Compulsory Revisions**

Q 1. Table 1 should have data on both groups (adherent and non-adherent) instead of the total dataset. In addition, statistical comparison of all parameters for both groups should be performed, and significant differences pointed out.

   = We have corrected in accordance to your suggestion

Q 2. The authors describe at the end of page 6 (results section) the characteristic of household income from the caregivers, and cite table 1. However, table 1 does not have information on household income, it should be included in the table.

   = We have corrected in accordance to your suggestion

Q 3. Finally, Table 1 should also include data on the time of exposure of each group. Authors state that the inclusion criteria of the study had children that were on ARV therapy at least for 12 weeks prior to the survey. However, it is not clear whether differences were observed in total time of treatment between the adherent and the non-adherent groups. This is very important since the authors discuss the effect of time of ARV treatment on adherence in the Discussion section.

   = The data on the time of exposure is included in table 1

Q 4. Table 2 contains data on provider’s estimate of adherence, which makes much more sense to be in Table 1. Table 2 depicts only clinical markers of the study.

   = We have corrected in accordance to your suggestion

Q 5. The parameters in Table 2 should be statistically tested for differences between the two groups analyzed (adherent X non-adherent).

   = We have corrected in accordance to your suggestion

6. One of the parameters evaluated in the study was the attitude of the caregivers toward the administration of ARV to children. This was classified as “favorable” or
“unfavorable”. However, the definition of these values for the variable is not described anywhere in text. It should be included in the Methods section.

= Included in the corrected version of the manuscripts under operational definitions.

7. A better categorization of adherence levels could be performed, for example the number of doses taken. Authors could use the categories 100%, 100-75% and less than 75%.

= Almost all studies we are comparing with and most literatures define adherence as “a child is said to be adherent if he/she missed no more than one dose (took more than 95% of the prescribed doses correctly) for one week prior to the study.” Due to these we preferred to use this definition as it is widely used adherence definition.

8. Was there any difference observed among the four drug schemes utilized? Particularly between the use of NVP X EFV?

= there’s no observed difference on adherence and the drug scheme. It can be seen from table 2(P= 0.105)

9. Authors should discuss the issue of the caregivers’ belief in the benefits of drug treatment to their children, since 10% of them did not believe in the drugs. This appears to be a major issue for future intervention in public programs of population awareness.

= In fact only 10(2.6%) caregivers did not believe in the drugs (See Table 1).

10. Authors should also discuss the fact that NNRTI-containing regimens are more prone to adherence than other HAART regimens. This is widely evidenced in the literature.

= It is correct that NNRTI containing regimens are more prone to adherence than other drugs. However drug regimens related factors are not predictors of adherence in this research finding.

Minor Essential Revisions

11. English and typographical errors should be revised throughout the manuscript. English is poor and there are multiple typographical and lexical errors in the text, and also inappropriately capitalized words.

= Native speakers edited the manuscript.
12. Several abbreviations are not explained in the text, such as “FA” (page 8) and “PLHIVs” (page 10). Please provide terms in full, especially since they are not used more than once in the text.

Reviewer's report

Reviewer: Elaine J Abrams

Abstract

Page 2 “Adherence to HAART in children in Addis Ababa was higher than other countries. This is a broad generalization.” Need to clarify-self reported adherence and compare to similar setting.

== Improved accordingly under conclusion.

“Nutritional supports, disclosure of child Sero-status, uses of co-trimoxazole’s as prophylaxis are essential to improve adherence to ART among children.” Need to work on the sentence, it implies that provision of nutritional support, and disclosure of HIV status can improve adherence which is not the conclusion from the study.

== Improved accordingly under conclusion during edition.

Background

Page 3 “Of this, 2.5 million children aged 0#14 years were infected with HIV in 2007.” This is not the number of new infections in 2007; it is the number of children living with HIV. The correct number is 420,000 per UNAIDS epi update 2007

=== Corrected according to UNAIDS 2007 report.

Page 3 “However, every day there are nearly 1500 new infections in children under 15 years of age.” This should be 1200 per UNAIDS epi update 2007.

== Corrected

Participants

Page 4 “Children who fulfill the following criteria were included in the study: Receiving continuous antiretroviral therapy for the last 12 weeks before study in the selected hospital and the caregiver was Parents or guardian that was counseled on the importance of drug adherence and on how to recognize common adverse drug reactions associated with antiretroviral drugs.”
Is this the only inclusion criteria? Is this the standard of care or does it represent specialized adherence support?
Should clearly state exclusion criteria. How was consent obtained? Written or verbal?
Were children interviewed? Are there any legal restrictions around enrolling non-biologic parents in studies?

== Yes, for this study the inclusion criteria were those listed. In the revised manuscripts we also added the exclusion criteria. Verbal informed consent was taken from the caregivers.

=In this study, children were not interviewed. Only caregivers of the children were asked on the circumstance of the issue. Both biological and non-biological parents were included depending on the close proximity with child.

Measurements
Page 4 “Data was collected by structured questionnaire. The questionnaire was originally developed in English.” Have the questions been validated elsewhere? Was it translated into local language before it was used? What type of questions, open ended? Were any of the common pediatric questionnaires employed in other studies used or adapted? Were older children interviewed or only caregivers?

== the questionnaire was adapted from the reference cited under measurement part and additional questions were also added from different body of literature. The final English version of the questionnaire was translated into Amharic by another person who is blind for the original questionnaire. As depicted above, only caregivers were asked.

Page 5 “Charts were reviewed to collect clinical and virological markers of the children.”
Does this include viral load data? Is VL available for this analysis?
= we collected CD4 count VL data was not available for our review.

Result
Page 6. “The majority 205 (52.6%) of the children was above 9 years. The mean and median age of the children were 3.33 and 4 years (range: 1 to 4 years)”. The range seems incorrect if half of the children were > 9 years of age.
= corrected in the recent manuscripts (It was done with categorized data).
Page 6 “About 277(71.4%) of the respondents had household income level below <=500 Eth. Birr.” It will be good if the authors gave the equivalent in USD or Euros.

Why is religious affiliation important?

Religious beliefs and practice affect adherence to ART. Such as “holy water” which can not be used with the modern medicine. In addition fasting may interfere with adherence to ART.

Page 7 “For those who missed a dose or more in the last 7 days, the common reasons were lack of medication (27.5%), child slept (25.5%) and forgetfulness to give the drugs (23.5%). (See Figure 2)” the authors need to explain what is meant by lack of medication- drug run out at home or pharmacy stock out or no transportation to go to hospital to refill meds? Also need to clarify forgetfulness, is this on the part of the caregiver or the child?

Page 7 “As shown in the above table, after controlling other variables, children whose parents didn’t paid fee for treatment were 61.3% less likely to adhere for ART than those who paid for their medication [OR= 0.387(95%CI: 162,0.924)].” The confidence interval here is different from what is reported in the abstract and table 4. It is missing a decimal point.

Other issues: please evaluate the duration of therapy for participants. What is the mean number of days on therapy? Is duration of treatment related to adherence?

Discussion

Page 8 “Clinical record review, virological and Immunological markers and psychological and medication related factors were assessed along with the caregiver characteristics to determine the predictors of adherence.” The authors did not report viral load.
Page 8 “This study found an estimated prevalence of adherence to antiretroviral treatment to be 363(93.1%) in 3 days and 339(86.9%) in 7 days recall period.” The authors should state that this is self reported adherence.

== corrected accordingly in the new version.

Page 8 “Adherence rate in other studies showed a prevalence of 26 %( 22).” Suggest the authors delete this sentence since the next sentence gives a range which is more appropriate.

= amended accordingly with the reviewer’s suggestions.

Page 9 “In one study, fourteen (33%) caregivers had not disclosed the child’s HIV status to him or her, and they reported that the child did not suspect being HIV positive (40) ……… This finding should be recognized and further investigation is needed in this regard.” This study from Uganda appears to contradict the findings in this paper. The authors should summarize and clearly make the point. There is too much unnecessary detail.

= We avoided the reference citation form the list. The core idea that we want to transfer from this research finding is that disclosure of the sero-status of the children is not related with adherence in children.

Page 11 “This could be probably due to the cross-sectional nature of the Study unlike clinical trail, and follow up design since the data is collected at one point in time might be depicted as reason.” Do the authors have a better explanation for the observed difference with the literature? Need to work on the grammar also.

= corrected accordingly.

Page 11 “Despite the above limitations, the study had several strength including use of both qualitative and qualitative methods for triangulation, inclusion of several sites, use of more than one method of adherence assessment and inclusion of several variables.”

This study used only one method to assess adherence- self report. There was no triangulation of methods

= Corrected

On Illustrations, tables and figures part
Page 19 Figure 1 is not relevant to the results. = corrected

Page 19 Figure 2 need to clarify if the caregiver or child forgot, what does run out of medications mean? = Corrected
Page 20 Table 1 add HIV disclosure status if available= Added.
Page 21. Table 2. Provider estimate of adherence is rated good, fair and poor (was this a visual analogue scale) and is compared to what was calculated based on the questionnaire? It will be useful to add data on viral load if available
= it is worthily mentioned under operational definitions and similar to the prepared questionnaire. For the case of viral load, as this research is carried out in resource limited country, VL is not utilized in clinical practice.

Minor Essential Revisions:
1. Failure to defines terms used e.g., HAART, MEMS, FA, ARV, write out names of medications before using abbreviations
   = corrected accordingly
2. More thorough editing and correction of spelling and grammatical errors would be useful.
   == edited by native speakers.

Reviewer's report
Reviewer: Philippe Msellati

# Major Compulsory Revisions
The results are so surprising and systematically in opposition with what we know on this topic that I ask the authors to check again their analysis and especially the multivariate analysis. As a naive reader, I could think data have been inverted.
On the same statistic side of the paper, I am wondering how authors obtain such figures ? "The majority 205 (52.6%) of the children was above 9 years. The mean and median age of the children were 3.33 and 4 years (range: 1 to 4 years)."
It is really surprising result for us also, however we cheked repeatedly for the data and consulted experienced statistician and the data is not inverted. The mean and median age are corrected.

# Minor Essential Revisions

Please change:

First, descriptive statistics was carried out to explore the socio-demographic "characterises" of the respondents, the adherence rate and clinical "characterises"

"Despite the above limitations, the study had several strength including use of both qualitative and qualitative methods for triangulation, inclusion of several sites, use of more than one method of adherence assessment and inclusion of several variables."

Authors may have meant quantitative and qualitative methods

I am not sure that figure one is absolutely necessary

"Over all, the participant attitudes on administration of ARV medication to the children were favorable in 380(97.4%) of the respondents with a 12 points liker scale instruments"

Could we have more details on the used scale?

No use of three digits after dot, two should be enough and less confusing

"Children who didn’t know their Sero-status were 2.53 times more likely to adhere for the treatment of ARV than children who didn’t know their sero status”

Could authors check that sentence?

=Corrected