Author’s response to reviews

Title: Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study.

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Author’s response to reviews: see over
Dear editor and reviewers

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Thanks you for reviewing this manuscript and for the opportunity to submit a revised paper. The manuscript has been changed to address the reviewers’ comments. Details of these changes and response to their concerns are described in this letter.

Sample size

A paragraph has been added to the “analysis” section of the “Methods” concerning sample size calculation and the reason that sample size was limited.

“At the time that the study was designed, few data on paediatric adherence from resource-constrained countries were available on which to base sample size calculations. The change from donor-funded ART to the government ART program necessitated ending of the study as the government program did not fund adherence monitoring. By this stage the accumulated sample size was sufficient to detect a 50% reduction in proportion with viral suppression in those with MR adherence <90% with 90% power, assuming that 75% of children had MR adherence ≥90%.”

In addition, a discussion of the limitations of the small sample size has been added to paragraph 4 of the “Discussion” section.

“The small sample in this study may also have reduced its power to show such an association particularly as a far smaller number of children than expected had poor adherence. In addition, the sample size limited the number of predictor variables that could be used in analytic models. We were only able to include a single indicator of disease severity in the model of viral suppression and only able to include socio-demographic and regimen factors as predictors of MR adherence ≥90%.”
Referee 2 (3568185991912355: Lauren V. Wood)

Minor essential revisions:
1) The words “of caregivers” have been added to the abstract as requested.

2) The footnote indicating the percentage of children in whom medication was returned on every possible occasion has been added to figure 1. Since 50% of children returned medication on every possible occasion, the median number of returns is 12, the total possible number of returns.

3) The x-axis label for figure 2 has been changed as requested.

4) The y-axis label for figure 3 has been changed as requested.

Discretionary revisions
1) The abstract has been amended to include the lack of association between MR adherence ≥90% and immunological response to ART as follows:

   “Ninety-one (79%) children achieved annual average MR adherence ≥90%. This was an important covariate associated with viral suppression after adjustment for disease severity (OR=5.5 [95%CI: 0.8 – 35.6], p=0.075), but was not however associated with immunological response to ART.”

2) The reviewer considers the finding that weight-for-height z-score correlated with MR adherence ≥90% very important. Unfortunately, it is difficult to establish whether the association between weight-for-height z-score and adherence is a true one, or whether it is confounded by other factors. Low weight-for-height z-score is also associated with younger age with those <2 years of age having a significantly lower median weight-for-height z-score compared to older children (p=0.001). Children less than 2 years of age are more likely to be taking a regimen including ritonavir (p<0.001), and we showed that children on ritonavir were significantly less likely to have MR adherence ≥90% (Table 3). Unfortunately the small sample size did not permit us to include both clinical, regimen and socio-demographic characteristics in our model of predictors of poor adherence, hence we were unable to determine the unconfounded effect of weight-for-height z-score on adherence. Indeed, after
adjustment for socio-demographic factors (access to water and electricity and education of the caregiver) and ritonavir-containing regimen, weight-for-height z-score was not associated with MR adherence \( \geq 90\% \). We have therefore not added this finding to our abstract.

3) The figure has been added as figure 3 as requested. The following sentences have been added to paragraph 2 of the results to describe the figure:

   “The number of children remaining in care at each month and the proportion returning medication as requested is shown in figure 3. There was no change in the proportion of children returning medication over time (p=0.17).”

In addition, the following sentence has been added to paragraph 4 of the results section to address the issue of whether there is a cutoff # of MR return months that correlates with clinical outcomes:

   “Similarly no association was found between the proportion of visits in which caregivers failed to return medication and viral suppression in either univariate or adjusted analyses.”

4) The effect of drug formulation is addressed in paragraph 5 of the discussion of the originally submitted manuscript. The wording of this paragraph has been changed to clearly state that we acknowledge that failing to record drug formulation is a limitation of this study.

5) The sentence: “Although we did not examine the effect of complex dosages and dosage changes on MR adherence, the positive impact on adherence in children of better education and socio-economic status of their caregivers is not surprising.” has been added to the last paragraph of the discussion to address the issue of dosing on adherence.

6) The following sentence has been added to paragraph 1 of the methods section to clarify the social criteria used when determining eligibility for ART.

   “In addition, the following limited social criteria needed to be met: having an identifiable caregiver to administer medication and attend clinic appointments; resident in Cape Town for at least 3 months; caregiver compliance with last 3 clinic appointments and caregiver willingness to comply with ongoing regular clinic attendance and monitoring.”
In addition, we have added the sentence: “In addition, the social criteria used to determine ART eligibility may have further selected those patients more likely to be adherent.” to paragraph 2 of the discussion to acknowledge that this selection bias as a limitation of the study.

7) The following sentence has been added to the last paragraph of the results section to address the issue of a potential association between caregiver education and socio-economic status:

“Having secondary education was not associated with any of the indicators of socio-economic status.”

In addition, the following sentence has been added to the last paragraph of the discussion:

“The lack of association between caregiver education and any of the indicators of socio-economic status emphasizes that these both impact on adherence and one is not simply a surrogate marker of the other.”

8) Paragraph 5 of the discussion has been split into 2 paragraphs and the following has been added to the second of these paragraphs:

“It is further noteworthy that MR adherence results in the ritonavir group appear paradoxical: taking ritonavir was both negatively associated with (capped) MR adherence ≥90%, and positively associated with (uncapped) MR adherence >100%. The excess adherence is explained by frequent need for repeat dosing. However poor adherence in the ritonavir group when measures are capped indicates that there is not always compliance with frequent dosing with an unpalatable drug ultimately impacting negatively on adherence. Indeed the poor adherence in the ritonavir group was attributable to poor adherence to ritonavir alone, with adherence to the other two drugs in the regimen being acceptable (data not shown).”

This explains how we reconcile the different findings with respect to adherence in the ritonavir group when using the capped and uncapped measures.
Referee 1 (1216667211879691: Catherine Orrell)

Discretionary revisions

Abstract: The abstract has been changed as follows to clarify the outcomes of those no longer in care at 3 months:

“By 3 months 13 (10%) children had deceased and 11 (10%) were lost to follow-up. Questionnaires were completed by 87/98 (90%) of caregivers of those who remained in care.”

Methods, paragraph 5: As the reviewer suggests, adherence >100% was only recorded if children required additional doses or there was spillage of syrups. The paragraph has thus been amended to clarify this.

“A small amount of extra medication (in excess of what was prescribed) was issued at each visit so that patients would not be without medication if drugs were spilled or additional doses required due to vomiting or spitting out. For a number of medication returns, therefore, more drug was used than prescribed (i.e. adherence >100%) so adherence was capped at 100% per return when calculating annual average adherence.”

Results paragraph 2: The caption for figure 3 (now figure 4) has been amended to emphasize that only children who remained in care for the full year of treatment were included in the analysis. This is precisely to prevent artificial apparent improvement of adherence figures by including children who subsequently became LFU in the adherence figures for the earlier months. In addition, the wording of the sentence in paragraph 2 that refers to this figure has been similarly amended as follows:

“Among only those children who remained alive and in care for the entire first year of treatment (excluding those deceased and LFU; n=88), the proportion with adherence <90% decreased over time with an OR for having low adherence of 0.91 (95% CI: 0.87 – 0.96; p=0.000) for each additional month (figure 4).”
Results paragraph 2: The wording of the sentence has been changed to make the meaning clearer.

“Annual average MR adherence <90% was more likely among the 34/115 (30%) child-caregiver pairs who failed to return empty medication containers/unused medication at more than one follow-up visit (OR=4.97; 95% CI:1.92 – 12.87; p=0.001). “

Minor essential revisions:
Methods 1st paragraph, 5th sentence. The reference number has been moved as required.

Referee 3 (1704892522207292: Carlo Di Pietrantonj)

Discretionary revisions
We have retained these figures (2 and 3) as we feel they convey information in a more succinct and clear manner than the text and are key findings of our paper. The suggestion to drop these figures is also in conflict with the request from reviewer 2 to add an additional figure of this genre to the manuscript. We would not however object to them being removed at the editor’s discretion.

Minor essential revisions
The top of figures has been changed to 100% as requested.

We look forward to your response to our revised article. Please contact us at Mary-Ann.Davies@uct.ac.za should you have any queries with regard to this manuscript or require any additional revisions.

Yours faithfully
Mary-Ann Davies (on behalf of all authors)