Author's response to reviews

Title: Pharmacy refill adherence outperforms self-reported methods in predicting HIV therapy outcome in resource-limited settings

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Version: 2 Date: 13 June 2014

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RESPONSES TO REVIEWER’S COMMENTS

Dear Editor:

We are pleased to resubmit for publication the revised version of MS: 4761922921262398 “Pharmacy refill adherence outperforms self-reported methods in predicting HIV therapy outcome in resource-limited settings”. We would like to thank the editor and both referees for constructive review and helpful comments on this manuscript. We have addressed each concern as outlined below, and highlighted the changes in the manuscript.

Yours sincerely,

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RESPONSES TO REVIEWER’S COMMENTS

Reviewer 1
Minor Essential Revisions
1. Title page: there seems to be more than two institutional address but only two of them were indicated in the title page.

RESPONSE: We apologize for this omission, the other institutions which were previously only under section of author details are now included in the title page as well.

2. Abstract: the abstract reflects the findings of the study and properly summarized.

RESPONSE: We are grateful that the reviewer found the abstract sufficiently summarized the manuscript.

3. Introduction: Most of the statements in first paragraph needs to be referenced. Currently they lack reference. The rest is well written and justifies the importance of the study.

RESPONSE: We are sorry for the lack of clarity of references in the first paragraph. We have now indicated references for this section. Page 4 line 84 to 92.

4. Methods: The selection of the sampling should be clearly stated as it is convenient sampling. In addition there should be a justification for 254 or 220 sample size, currently nothing was mentioned how the authors arrived at this sample?

RESPONSE: We are sorry for the lack of clarity of regarding the selection method. Due to budget restrictions, the study was carried out as an exploratory study to inform larger studies when needed, hence convenient sampling was undertaken without sample size calculation.

In the first paragraph in methods we have indicated that patients were conveniently sampled in the window period for patient recruitment. Moreover, in figure 1 we have indicated how we started with 254 patients and remained with 220 patients with adherence measurements and finally 162 patients with viral load measurements at both the start and the end of the study.

We have added to the first paragraph of discussion section the following statement “This study was carried out as an exploratory study using convenient sampling, and can thus serve to inform larger studies on pharmacy refill adherence as a predictor for virological treatment response”. Page 16 line 378-380.

5. The rest of the methods and the result sections are well described.

RESPONSE: We are grateful that the reviewer found the rest of methods and results sections sufficiently covered in the manuscript.

6. It would be helpful to see at least one ROC curve for the best performing measurement.

RESPONSE: We thank the reviewer for this useful comment we have included additional file 5, which is the ROC curve for pharmacy refill adherence measurement in predicting virological failure at adherence thresholds between 50 and 100. The curve denotes an increase in the area under the curve with increasing cut-off until optimum at 95%. Page 34 line 768-773 and cited at page 14 line 336.
7. Discussion: Is well written and discuss the findings very well.
RESPONSE: We are grateful that the reviewer found the discussion section sufficiently covered in the manuscript.

Reviewer 2
Minor Essential Revisions: None:
RESPONSE
We thank the reviewer for taking time to review our manuscript and commending the usefulness of the work we have done.

Editor's Comments:
1. Please clearly describe the follow up strategy. How often were the follow up.
RESPONSE: We are sorry for omission of information on the follow up strategy. We have added the following statement at the first paragraph of methods
"Patients on ART are normally scheduled to return for antiretroviral (ARV) pick-ups at least once monthly. During the visit they also consult with the clinician after receiving adherence counselling from the nurses. CD4 T-cell counts measurements are taken at least every 6 months". Page 7 line 158-161. In the adherence measurement section of the methods we had already indicated that Adherences measurements were taken at 4 time-points during a one year follow-up including at recruitment (0), 1st, 2nd and 12th months after recruitment.

2. In the method, cox regression was mentioned but all the findings and tables are related to logistic regression.
RESPONSE: We thank the editor for seeking clarification and we apologize for lack of clarity with regard to cox-regression. The Cox regression was mentioned under the results section “Kaplan-Meier and Cox model for immunological recovery” and discussed thereafter.

3. Please answer the reviewer comments line by line including the sampling methods and sample size.
RESPONSE: we appreciate all your comments. We worked hard to respond the comments of reviewers as indicated above and those of the Editor (below). Thank you for taking the time and energy to help us improve the manuscript. We hope that these changes have made it more appropriate for publication, and we look forward to your response.

Additional Editorial Requests:
1.) Copyediting
   We recommend that you copyedit the paper to improve the style of written English
RESPONSE: Thanks to the Editor for recommending copyediting the manuscript in order to improve readability. We have consulted and adjusted several statements that were unclear in the text. However, due to budget restrictions we were not able to solicit an external professional English editor. The changes are highlighted in the text;
Our aim was to investigate the best performing adherence measurement method for predicting virological failure in resource-limited settings (RLS).

Additionally, the adherence models were evaluated by fitting multivariate LR with stepwise functions, decision trees and random forests models, assessing 10-fold multiple cross validation (MCV).

Viral load measurements at baseline and at one year after recruitment were available for 162 patients.

Widespread antiretroviral scale-up programs are taking place in resource-limited settings (RLS).

There is sufficient international evidence to support that adherence to combination ART is a major predictor of viral suppression.

Settings, affordability and low staff requirements. Self-report has consistently been correlated with viral load.
Page 6 line 128-129 was changed from “Manual pill count is a cheaper and easier alternative to estimate dosages taken. It is limited by the intensive need of staff” to “Manual pill count is a cheap and easy alternative to estimate dosages taken. However, it is limited by the intensive need of staff”.

Page 8 line 187-188 was changed from “Each refill period was identified as the interval between the last visit date and the scheduled new refill date” to “Each refill period was identified as the interval between the last visit date and the scheduled refill date”.

Page 9 line 197 -198 was changed from “Patients responded to a questionnaire asking questions regarding the number of dosages missed over the period of the past one month” to “A self-report questionnaire was administered to patients to assess missed dosages over the past one month.”

Page 9 line 210 was changed from “pills in the previous visit was calculated based on the dose and the number of days dispensed” to “pills during the previous visit was calculated based on the dose and the number of days dispensed”.

Page 10 line 232 was changed from “viral load measurement, while 1,000 represent a virologic cut-off widely used to perform genotyping” to “viral load measurement, while 1,000 represents a virologic cut-off widely used to perform”.

Page 11 line 251 was changed from “were performed using R-statistical package version 2.15.” to “were performed using the R-statistical package version 2.15.1”.

Page 11 line 257 was changed from “outcome, an immunological outcome and adherence data at the 1 year time point and included in this study” to “outcome, an immunological outcome and adherence data at the 1 year time point and were included in this study”.

Page 12 line 269-270 was changed from “patients had significantly more often a CD4 T cell count measurement performed, 8 (6-11) times compared to 7 (4-11) times in the excluded group
(p-value = 0.03).” to “patients had a CD4 T cell count measurement performed significantly more often than the excluded group; 8 (6-11) times compared to 7 (4-11) times (p-value = 0.03).”.

Page 18 line 422-423 was changed from “Even though in our hands the optimal cut-off for pharmacy refill is 95%, the dose response relationship shown in the comparison virological outcome and grouped pharmacy refill adherence” to “Even though in this study the optimal cut-off for pharmacy refill is 95%, the dose response relationship shown in the comparison of virological outcome and grouped pharmacy refill adherence”.

Page 26 line 668 was changed from “Final included patients were those with both baseline and follow-up viral load” to “. Only patients with viral load data at baseline and follow-up were included in the final analyses.”