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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RESPONSES TO EDITOR’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 for the 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 EDITOR COMMENTS

Editor's Comments:

"The authors shall do thorough revision on the paper to avoid any typographical and grammatical errors: e.g
-Avoid 'our aim.... in the abstract. it can be replaced by the objective of the study......
-The result section needs several revision. Particularly under cox regression, the sentences are not clear and attractive."

RESPONSE: We followed the advice of the Editor with regard to the recommended changes in the document, a summary of which can be found below

Page 3 lines 49-50 were changed from “Our aim was to investigate the best performing adherence measurement method for predicting virological failure in resource-limited settings (RLS)” to

“The objective of the study was to investigate the best performing adherence assessment method for predicting virological failure in resource-limited settings (RLS)”.

Page 16 lines 368-377 were changed from “Kaplan Meier survival analysis was done with months as the time unit, in order to assess the time taken by patients to recover CD4 T cell count by at least 50 or 100 cells/µl (Figure 3). Patients who had a pharmacy refill adherence of < 95% recovered 50 and 100 cells/µl in a median (95% confidence interval) of 5 (4-8) and 8 (5-10) weeks, respectively, while patients who were > 95% refill adherent, recovered in 4.5 (4-6) and 7 (6-9) weeks, respectively. Although the median time to reach the increment was longer in non-adherent group, this difference did not reach significance (logrank p = 0.15 and 0.23 for increment of 50 and 100 cells/µl, respectively). When combining pharmacy refill adherence with age, gender and CD4 T cell count at baseline, a Cox regression analysis resulted in significant differences (Wald test p < 0.01)” to “Kaplan Meier survival and Cox regression analysis was performed with months as the time unit, in order to assess the time taken by patients to recover CD4 T cell count by at least 50 or 100 cells/µl (see Figure 3). Patients who had a pharmacy refill adherence of < 95% recovered 50 and 100 cells/µl in a median (95% confidence interval) of
five (4 - 8) and eight (5 - 10) weeks, respectively, while patients who were > 95% refill adherent recovered in 4.5 (4 - 6) and seven (6 - 9) weeks, respectively. Although the median time to reach the increment was longer in the non-adherent group, this difference did not reach significance (log rank p = 0.15 and 0.23 for increment of 50 and 100 cells/µl, respectively). However, when pharmacy refill adherence was combined with age, gender, and CD4 T cell count at baseline, a Cox regression analysis resulted in significant differences (Wald test p < 0.01)

Additional Editorial Requests:

1.) Copyediting

We recommend that you copyedit the paper to improve the style of written English.

RESPONSE: We followed the advice of the Editor with regard to the recommended copyediting of the manuscript in order to improve readability. We solicited an external professional English editor. The changes are highlighted in the text;

Page 3 lines 49-50 was changed from “Our aim was to investigate the best performing adherence measurement method for predicting virological failure in resource-limited settings (RLS)” to “The objective of the study was to investigate the best performing adherence assessment method for predicting virological failure in resource-limited settings (RLS)”.

Page 3 line 52 was changed from “This was a single-centre prospective cohort study enrolling 220 HIV-infected adult patients” to “This study was a single-centre prospective cohort, enrolling 220 HIV-infected adult patients”.

Page 3 line 52 and all over the document as highlighted

Several comma punctuations were introduced.

Page 3 line 54 was changed from “refill, self-report (visual analog scale (VAS) and the Swiss HIV Cohort study-adherence questionnaire)” to “refill, self-report (via visual analog scale [VAS] and the Swiss HIV Cohort study-adherence questionnaire)”
Page 3 line 55 was changed from “pill count and appointment keeping adherence measurements were investigated” to “pill count, and appointment keeping adherence measurements were taken”.

Page 3 lines 64-65 were changed from “of which 34% had detectable viral load and 10.5% had immunological failure at one year” to “of whom 55 (34%) had detectable viral load and 17 (10.5%) had immunological failure at one year after recruitment”.

Page 3 lines 64, 66 and all over the document as highlighted
Several occurrences of the % symbol, a space was added to separate it the preceding number.

Page 4 lines 71-72 were changed from “univariate adherence models, except pharmacy refill adherence univariate model was comparable to the multivariate model (AUC=0.64)” to “univariate adherence models, except pharmacy refill adherence univariate model, which was comparable to the multivariate model (AUC = 0.64)”

Page 4 line 74 was changed from “Pharmacy refill adherence (<95%) emerged as the best method predicting virological failure.” to “Pharmacy refill adherence (<95%) emerged as the best method for predicting virological failure”.

Page 4 line 88 was changed from “virological outcome is recommended because of its good correlation with therapy success in” to “virological outcome is recommended because of its strong correlation with therapy success in”.

Page 5 line 99 was changed from “Strategies to measure adherence to ART include Medication Event Monitoring System (MEMS),” to “Strategies to measure adherence to ART include the Medication Event Monitoring System (MEMS),”.

Page 5 lines 104-105 were changed from “MEMS is widely used in clinical studies while pill count, self-report and pharmacy refill are widely used in the context of HIV and AIDS” to “MEMS is widely used in clinical studies, whereas pill count, self-report, and pharmacy refill are widely used in the context of HIV and AIDS”.
Page 6 line 130 was changed from “recommended by WHO as surrogate markers for emergence” to “recommended by the World Health Organization (WHO) as surrogate markers for emergence”.

Page 7 line 152 was changed from “The present study aimed to validate an instrument capable of” to “The objective of the current study was to validate an instrument capable of”

Page 8 lines 162-173 were changed from “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. Two hundred and fifty four patients were invited into the study during the months May and July 2010. Selection criteria were either starting ART or being on ART. Patients were conveniently sampled, continuously recruiting patients referred by nurse counsellors who are the first contacts at the clinic. Each day 10-15 unselected patients were recruited into the study. Exclusion criteria were being below 18 years, pregnant, having opportunistic infections or malignancy. Of the 254 patients recruited into the study, 34 were excluded from analysis for various reasons (Figure 1). The remaining 220 provided adherence information and were followed for a period of one year. The herein presented study included 162 patients who completed 1 year follow-up and had their adherence, immunological and virological outcomes monitored over the entire period.” to “During the visit, they also consult with the clinician after receiving adherence counselling from the nurses. CD4 T-cell count measurements are taken at least every six months. Two hundred and fifty-four patients were invited into the study during the months of May to July, 2010. Selection criteria were either starting ART or being on ART. Patients were conveniently sampled, as the study researcher continuously recruited patients who were referred by nurse counsellors, the first contacts at the clinic. Each day, 10-15 unselected patients were recruited into the study. Exclusion criteria were being younger than 18 years of age, pregnant, having opportunistic infections, or malignancy. Of the 254 patients recruited into the study, 34 (13.39%) were excluded from analysis for various reasons (see Figure 1). The remaining 220 provided adherence information and were followed for a period of one year. The herein presented study included 162 patients who completed a one-
year follow-up and had their adherence, immunological, and virological outcomes monitored over the entire period”.

Page 8 lines 176-181 were changed from “Virological and immunological outcomes were assessed at one year follow-up. These outcomes were dichotomized according to the following definitions. Virological failure was defined as having a viral load above the detection limit of 400 copies/mL. Immunological failure was defined according to the WHO guidelines as having either (i) a CD4 T cell count of 100 cells/µl six months post ART (ii) a CD4 T cell count of less or equal to CD4 pre-ART at six months on ART or (iii) 50% reduction from the on-ART peak CD4 T cell count” to “Virological and immunological outcomes were assessed at the one-year follow-up. These outcomes were dichotomized according to the following definitions: Virological failure was defined as having a viral load above the detection limit of 400 copies/mL; and immunological failure was defined according to the WHO guidelines as having (i) a CD4 T cell count of 100 cells/µl at six months post ART, (ii) a CD4 T cell count of equal to or less than CD4 pre-ART at six months on ART, or (iii) 50% reduction from the on-ART peak CD4 T cell count”.

Page 8 lines 185-186 and all over the document as highlighted
Several occurrences of numerals 1-9 was changed to one, two…nine.

Page 8 line 193 and all over the document as highlighted
Several occurrences of per cent were changed to percent.

Page 8 line 196 and all over the document as highlighted
Several occurrences of pick up were changed to pick-up.

Page 9 lines 198 were changed from “this gives the percentage of time the patient was without medication over the whole year” to “resulting in the percentage of time the patient was without medication over the whole year”.

Page 9 lines 201-202 were changed from “A self-report questionnaire was administered to patients to assess missed dosages over the past one month” to “The researcher for this study administered a self-report questionnaire to patients to assess missed dosages over the previous one month”.
Page 3 lines 205-211 were changed from “It consists of firstly, the visual analog scale (VAS) probing the percentage of doses taken in the previous month. Secondly, it probes two questions from the Swiss HIV Cohort Study Adherence Questionnaire (SHCS-AQ) regarding frequency of missed doses and ever missing two consecutive doses (drug holiday) in the previous month. By definition reporting missing at least one ARV dose or two consecutive doses in the month preceding the interview was scored non-adherent” to “This validated study tool consists of two major sections: 1) the visual analog scale (VAS), which probed the percentage of doses taken in the previous month; and 2) it probes two questions from the Swiss HIV Cohort Study Adherence Questionnaire (SHCS-AQ) regarding frequency of missed doses and if a patient ever missed two consecutive doses (drug holiday) in the previous month. By definition, reporting of having missed at least one ARV dose or two consecutive doses in the month preceding the interview was scored as non-adherent”.

Page 10 lines 221-223 were changed from “usually this amounts to one month. Appointment keeping was deduced from the medical records and database. A patient visiting on the scheduled appointment was scored as 100% appointment adherent, whereas if an appointment was skipped entirely, it was scored as 0% adherence” to “which usually this amounts to one month. Appointment keeping was deduced from the medical records and database. A patient visiting on the scheduled appointment was scored as 100% appointment adherent, whereas if an appointment was skipped entirely, it was scored as 0%”.

Page 10 line 231 was changed from “starting from 100% going down to 50% in steps of 5” to “beginning with 100% and decreasing to 50% in steps of 5”.

Page 10 lines 232-238 were changed from “such that patients with adherence below the cut-off were classified as non-adherent, the others were classified adherent. The trade-off for sensitivity and specificity was analysed upon changing the adherence cut-off to predict virological failure at 12 months, dichotomized using two different viral load cut-offs: > 400 copies/mL, or > 1,000 copies/mL. The 400 copies/ml virological cut-off is the detection limit of our viral load measurement, while 1,000 represents a virologic cut-off widely used to perform genotyping” to “such that patients with adherence below the cut-off were classified as non-adherent, the others were classified adherent. The trade-off for sensitivity and specificity was analysed upon changing the adherence cut-off to predict virological failure at 12 months, dichotomized using two different viral load cut-offs: > 400 copies/mL, or > 1,000 copies/mL. The 400 copies/ml virological cut-off is the detection limit of our viral load measurement, while 1,000 represents a virologic cut-off widely used to perform genotyping”.
“such that patients with adherence below the cut-off were classified as non-adherent, whereas the others were classified as adherent). The trade-off for sensitivity and specificity was analysed upon changing the adherence cut-off to predict virological failure at 12 months, which was dichotomized using two different viral load cut-offs: > 400 copies/mL or > 1,000 copies/mL. The 400 copies/ml virological cut-off was the detection limit of this study’s viral load measurement, while 1,000 represented a virologic cut-off widely used to perform genotyping”.

Page 11 lines 250-252 were changed from “Kaplan Meier survival analysis was used to find the difference between the time taken to increase the CD4 T-cell count by 50 cells/µl or by 100 cells/µl between adherent and non-adherent patients. Cox regression analysis was used to adjust for confounding factors like age” to “Kaplan Meier survival analysis was used to determine the difference between the time taken to increase the CD4 T-cell count by 50 cells/µl or by 100 cells/µl between adherent and non-adherent patients. Furthermore, Cox regression analysis was used to adjust for confounding factors like age”.

Page 11 line 264 and all over the document was changed the citation of Figure and table “Figure 1” or “Table 1” to “(see Figure 1)” or “(see Table 1)”

Page 12 lines 283-318 several changes were made as highlighted in text

Page 12 line 320 was changed from “In univariate LR analysis odds of virological failure were determined. We found that being able to” to “In univariate LR analysis, odds of virological failure were determined. The study suggests that being able to”.

Page 12-15 lines 321-365 several changes were made as highlighted in text.

Page 16 lines 368-377 were changed from “Kaplan Meier survival analysis was done with months as the time unit, in order to assess the time taken by patients to recover CD4 T cell count by at least 50 or 100 cells/µl (Figure 3). Patients who had a pharmacy refill adherence of < 95% recovered 50 and 100 cells/µl in a median (95% confidence interval) of 5 (4-8) and 8 (5-10) weeks, respectively, while patients who were > 95% refill adherent, recovered in 4.5 (4-6) and 7
(6-9) weeks, respectively. Although the median time to reach the increment was longer in non-adherent group, this difference did not reach significance (logrank p = 0.15 and 0.23 for increment of 50 and 100 cells/µl, respectively). When combining pharmacy refill adherence with age, gender and CD4 T cell count at baseline, a Cox regression analysis resulted in significant differences (Wald test p < 0.01) to Kaplan Meier survival and Cox regression analysis was performed with months as the time unit, in order to assess the time taken by patients to recover CD4 T cell count by at least 50 or 100 cells/µl (see Figure 3). Patients who had a pharmacy refill adherence of < 95\% recovered 50 and 100 cells/µl in a median (95\% confidence interval) of five (4 - 8) and eight (5 - 10) weeks, respectively, while patients who were > 95\% refill adherent recovered in 4.5 (4 - 6) and seven (6 - 9) weeks, respectively. Although the median time to reach the increment was longer in the non-adherent group, this difference did not reach significance (log rank p = 0.15 and 0.23 for increment of 50 and 100 cells/µl, respectively). However, when pharmacy refill adherence was combined with age, gender, and CD4 T cell count at baseline, a Cox regression analysis resulted in significant differences (Wald test p < 0.01)".

Page 16-20 lines 380-479 several minor text changes and punctuations were made as highlighted in the discussion text.

Page 19 lines 482-491 were changed in the conclusion from “Of the adherence methods investigated we found that pharmacy refill method has the best performance in predicting virological failure. The performance improves when pharmacy refill adherence is combined with immunological response. We found this combination to have a reasonable sensitivity (around 70\%) and specificity (around 60\%) to predict virological failure. This combination can be useful to flag patients at risk for virological failure. It appears to be more reliable than immunological and clinical response alone and is cost-saving. Thus, it has the potential for a wider application in ART follow-up in RLS. When combined with even more variables, such as treatment and demographic characteristics in the full LR model, the prediction still improves, however this may become less straightforward and may thus lose applicability in RLS where doctors have very little time to devote per patient” to “Of the adherence methods investigated in this study, pharmacy refill method had the best performance in predicting virological failure. The performance improved when pharmacy refill adherence was combined with immunological response. The study found, this combination to have a reasonable sensitivity (around 70\%) and
specificity (around 60\%) to predict virological failure. This combination could be useful to flag patients at risk for virological failure. It appeared to be more reliable than immunological and clinical response alone and was cost-saving. Thus, it had the potential for a wider application in ART follow-up in RLS. When combined with even more variables, such as treatment and demographic characteristics in the full LR model, the prediction still improved, however this may become less straightforward and may, thus, lose applicability in RLS where doctors have very little time to devote to individual patients.”

Page 21 lines 507-536 (author details and acknowledgements) several minor punctuations were made as highlighted in the text.

Page 21 lines 507-536 (author details and acknowledgements) several minor punctuations were made as highlighted in the text.

Page 26 lines 673-734 (List of Figures and list of Tables) minor punctuations were made as highlighted in the text.

Page 30 lines 738-802 (Additional materials) minor punctuations were made as highlighted in the text.