Author's response to reviews

Title: Risk factors for loss to follow-up prior to ART initiation among patients enrolling in HIV care with CD4+ cell count greater than or equal to less than 200 cells/uL in the multi-country MTCT-Plus Initiative: a cross-sectional study

Authors:

R Charon Gwynn (crg2128@columbia.edu)
Ashraf Fawzy (fawzy.ashraf@gmail.com)
Ida Viho (iv2129@columbia.edu)
Yingfeng Wu (yw2322@cumc.columbia.edu)
Elaine J Abrams (eja1@cumc.columbia.edu)
Denis Nash (dnash@hunter.cuny.edu)

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To the Editors of BMC Health Services Research:

We thank you for considering publication of our manuscript, reference number: MS 2069417019123002 (Title: Risk factors for loss to follow-up prior to ART initiation among patients enrolling in HIV care with CD4+ cell count ≥200 cells/µL in the multi-country MTCT-Plus Initiative: a cross-sectional study) in BMC Health Services Research, and we greatly appreciate the opportunity to revise and resubmit our manuscript.

We were encouraged by many of the reviewer comments regarding the importance our manuscript. We have carefully considered the comments from the reviewers, and responded point by point below. We have also have made revisions to the manuscript accordingly, and indicate these in our reviewer responses. Many of the reviewer comments and suggestions resulted in strengthening our manuscript, and for this we are grateful.

Please let me know if you require any additional information.

Sincerely,

R. Charon Gwynn

Responses to reviewers’ comments

Referee 1

1. The sample included anyone who had a CD4 count of >=200 and WHO clinical stage <=2 at enrollment and then follows this group forward for LTFU. Over time patients selected into the study would have become eligible for ART and this is potentially important to explaining losses-to-follow. However updated CD4 information was not included. What is the justification for not including this information? If updated CD4 data was available for a sub-sample, could a sensitivity analysis be performed to examine losses occurring by ART eligibility status as a time-dependent covariate?

Response: First, our analysis subjects were censored at the time they initiated ART, thereby accounting for that that patients becoming eligible for ART were contributing to loss to follow-up. Second, time-updated CD4 information was inconsistently recorded in the electronic record. Selecting the subset of patients with consistently updated CD4 data, given the differential length of follow up and lack of data completeness, would have resulted in a biased sample.

2. Is there the possibility of informative censoring? Specifically CD4 at enrollment is very likely to be related to the hazard of death and losses to follow up, such that traditional methods are not
appropriate. Losses may be occurring more often in the higher CD4 group because both ART initiation and death (censoring events) are more commonly occurring in the lower CD4 groups.

Response: The reviewer raises a legitimate concern that applies more to ART patients than to patients not yet eligible for ART. In fact, the concern for informative censoring was the rationale behind including only those patients with higher CD4 count (>200 cells/μL) and early stage disease thus limiting the amount for AIDS related morbidity and mortality among those who became LTF. Given that we: a) restricted the analysis to those with CD4>200 at enrollment and b) censored patients who initiated ART, the proportion LTF in our sample was low (8%) and those LTF in our sample are probably more likely to be alive and either out of care or silent transfers, as opposed to HIV-related deaths. Despite this there is still potential for misclassification of deaths as LTF which is mentioned as a limitation of the study on page 13 line 4.

3. Were all women not pregnant at the time of enrollment? Why were some women who were not pregnant at baseline enrolling in a PMTCT program? Is this because some women were postpartum? How long since their delivery date, on average, were they enrolling in care? How relevant are these findings in the context of the expansion of B+?

Response: The MTCT-Plus program enrolled pregnant women (index women) and their family, and other household members. Non-pregnant women enrolled in the study were family members or household members of index women. As stated in the final paragraph on page 10 (continuing to the top of page 11), the findings from this work are very relevant in the context of B+ as pregnancy status, at enrollment and subsequent to enrollment, was a risk factor for LTF.

4. In the first sentence of the Discussion, the phrase “at enrollment” should be included following “who were not ART eligible.”

Response: We have made the suggested change.

5. In the methods section, there are 9 geographic locations mentioned and the text states that two programs in South Africa and Mozambique were excluded. In the results, however, there is information on 11 programs and these are listed in Table 1. The number of programs and geographic locations should also be clarified in the text.

Response: Two of these geographic locations had two clinical sites each for a total of 13 programs. This has been clarified on page 4 of the text to indicate that there were initially 13 programs.

Referee 2
Abstract

- Page 2, line 19: Delete the redundant word “with”

Response: Deleted the word “with” on line 19
Key words: None are given. These could be added
Response: Added keywords: HIV; AIDS; Anti-retroviral therapy; Lost to follow up; Risk factors; Social Support; pre-ART

Methods
- There is a 1-year period between observation period (ending March 31, 2007) and end of the MTCT-Plus Initiative period (ending March 31, 2008). The authors explain in lines 3-4 page 5 that the 1 year provides that an enrollee had at least 1 follow-up visit. At lines 9-12 it is noted that “patients with CD4>500 cells/mm3 were scheduled every 6 months, while those with CD4 between 200-500 cells/mm3 were scheduled every 3 months”. This means that within the 1 year (March 31, 2007 to March 31, 2008) patients with CD4>500 cells/mm3 would have a possibility of 1-2 visits and patients with 200-500 cells/mm3 a possibility of up to 4 times. Further, on page 5 line 12-13 “patients were considered LTF if their last clinic visit was at least 12 months prior to the end of data collection”. On page 6 line 1 “Patients meeting the LTF definition were considered to have exited the program 3 months after their last recorded clinic visit.” I think this reads a bit confusing. Are two definitions of LTF being used: “… last clinic visit was at least 12 months prior to the end of data collection” and “… 3 months after their last recorded clinic visit”?

Response: Patients whose clinic visit was 12 or more months prior to the end of data collection were considered LTF, regardless of their assigned visit schedule. The 3 month/6 month schedule criteria was provided as general contextual information about the program but was not used in the LTF definition. The paragraph on page 5 has been reorganized to try to clarify this point. The use of the 3-month criteria for the subsequent Cox regression analysis on page 6 was used in order to assign a time of LTF among those who met the LTF definition, however this does not relate to the definition of LTF.

- Page 4, line 20: Instead of “patients greater than 14 years old” why not “patients older than 14 years”
  Response: We have changed page 4 line 20 to “patients older than 14 years old”

- Page 4, lines 20-23: The grammar needs correction. A period could be set at the first part ending “MTCT-Plus programs (9 different countries).” And a new sentence begins with “We excluded two programs…”
  Response: We have split page 4 lines 20-23 into two sentences for clarity

- Page 5, lines 7-11: Make the WHO staging definition explicit.
  Response: We have changed page 5 lines 7-8 to “WHO clinical stage 1 or 2 (asymptomatic to moderately symptomatic) at enrollment” in order to be more explicit

- Page 5, line 19: Perhaps add “who” in “… women and all men who were either partners…”?
  Response: We have added the suggested text to page 5 line 19

Results
- **Page 7, line 21 and 22**: Add comma in the figures for consistency, thus “1,677” and “1,996”
  
  **Response**: We have made the suggested change to page 7 lines 21 and 22.

- **Page 8, line 2**: Clarify that the travel time means “within 1 hour of walk to the clinic”.
  
  **Response**: This is total travel time to the clinic. Revised here and throughout the manuscript.

- **Page 8, line 5**: “by definition” seems redundant as it is not explicitly explained prior, but I suggest to add here the definition from page 13 line 22 for better clarity so to have “by definition all had another family member enrolled, either as a husband, partner or household member”. The latter italicized text is only provided in this one instance in the current version of the manuscript and as such comes late in the paper.
  
  **Response**: We have clarified this in the text by splitting the paragraph starting on page 8 line 3 into two sentences and explicitly stating that all men had to, by definition, be a husband, partner, or household member of an index woman.

**Discussion**

- **Page 11, line 8**: This statement needs a qualification “LTF among pregnant women in HIV care will need to be addressed”
  
  **Response**: We have made the suggested change to page 11 line 8.

- **Page 11, line 9**: There is a missing term here “with qualitative studies have found that social”
  
  **Response**: We have corrected grammar on page 11 line 9.

- **Page 11, line 13**: This sentence “LTF rates in women with a household member enrolled was lower than that of men” seems inconsistent with Fig 1 and the interpretation given under Results page 8 lines 3-7.
  
  **Response**: This interpretation is consistent with the findings in the KM curve and the results presented in the text. LTF rates were lowest in women with a household member enrolled and highest in women without a household member enrolled. The paragraph starting on page 11 line 9 has been rearranged to better convey this interpretation. Mention of LTF rates in male participants has been omitted from discussion of the association of social support with retention since, as stated in that paragraph, we cannot comment on the impact of social support in men. Additionally the sentence that originally started on line 13 has been moved and rewritten to improve clarity of the paragraph.

- **Page 11, line 14**: Word “whose” seems redundant
  
  **Response**: This has been fixed by the previous edit.

- **Page 11, line 23 to page 12, line 1**: The claim “Social support systems are an integral part of managing patients care” is self-evident but a citation would validate it
  
  **Response**: We have added citation 28, DiMatteo et al.

- **Page 12, line 23 to page 13, line 3**: Two observations make this sentence confusing. (1) The first part “LTF to increase with year of enrollment” is consistent with Fig. 1, but which seems to be contradicted by the latter part stating “but our data did not reveal a consistent trend with year of enrollment”. (2) Is LTF expected to worsen with more clinical services as is implied with the half part of this sentence? This would seem contradictory as more services would usually mean more accessibility.
  
  **Response**: The assertion that LTF did not consistently increase with calendar year of enrollment
is based on data presented in Tables 3 and 4. Figure 1 is a person-time analysis, which describes retention by time since enrollment, which is different from calendar time. Figure 1 does not account for calendar year of enrollment and therefore cannot be used to make any assertions about the association between enrollment year and LTF. Furthermore, the statement that LTF would be expected to increase with enrollment year is based on the sentence on page 12 lines 19-22 which hypothesizes that with greater scale up of resources patients would preferentially seek care closer to their home (and be ‘silent transfers’ from the perspective of the clinic). The two sentences that originally spanned page 12 line 21 to page 13 line 3 have been rewritten to clarify that the stated hypothesis of increasing LTF with enrollment year relates to the fact that subjects would preferentially seek care closer to home as stated in the previous sentence.

- Page 14, lines 5-9: The “variations in LTF by facility” is a new finding being introduced here but not shown in the main Results or Discussion. While I do not find the mention in ‘Limitations’ problematic the variation by facility is, I think, a very important finding that, along with country variations, could warrant more analysis or discussion; unless, perhaps, the authors will be presenting this in a separate manuscript?

  Response: To clarify the sentence “facility” has been replaced by “site”. The differences in LTF by site is mentioned in the results section on page 7 line 5 of the original submission and presented in detail in Table 1. A reference to table 1 has also been added to the discussion section. We agree with the reviewer regarding the potential importance of this finding. However, as stated in the discussion paragraph cited by the reviewer, since we didn’t have systematically collected clinic/program-level information, a limitation of the study was that we were NOT able to identify reasons for the differences in LTF between sites due to lack of documentation about the site/program characteristics.