Author’s response to reviews

Title: PREDICTORS OF LOSS TO FOLLOW-UP AMONG CHILDREN ON LONG-TERM ANTI-RETROVIRAL THERAPY IN ZAMBIA (2003-2015)

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Dear BMC Editors:

Thank you for the thoughtful peer review of the manuscript (PUBH-D-18-00311) titled “Predictors of Loss to Follow-up Among Children on Long-Term Antiretroviral Therapy in Zambia (2003-2015)”.

We have responded to all the comments and substantially edited the manuscript to address all reviewer comments. Additionally we have changed the analytic method to include competing risks analysis to address a major weakness which was highlighted by one of the reviewers. We trust the changes and the additional analytic method adds more clarity to this important topic in the management of pediatric HIV. Please find below our responses to each of the very thoughtful and helpful reviews.

Heena Brahmbhatt (Reviewer 1):

Figure 3: the stats here are confusing. You state that lfu was highest during 1st 3 months where it was 4% and then say "losses decreased in 2nd year..." but the rate there is 11% and then state that by end of study period, losses were at 30%. So does lfu increase over time? Also, difficult to see where these numbers come from in Figure 3? Need to find better way of representing these data on the figure so its clearer

Figure 4: when looking at figure 4, it appears that the cumulative incidences for outcomes increase over time? perhaps have the 1st year expanded on the curve so the loss to follow up that is higher in 1st year is clearer

Response: The Kaplan-Meier estimate maybe biased when there are competing risks and this is clearly shown in our study. We decided not to present the KM analysis but instead present our results from the competing risks analysis. In the competing risks model, cumulative incidence of LTFU increases over time and the interpretation is much clearer than findings from the KM approach. We have since made changes to the manuscript and describe the analysis in the methods section, page 8 line 10-21.

The cumulative incidence curve (Figure 2) shows that cumulative incidence increased over time. The slope on Figure 2 is cumulative incidence. The steepness of the slope reflects the rate at which the cumulative incidence increased. During the first year, we see that the slope is very steep and this implies that cumulative incidence was highest during the first year. We present the pointwise estimates and 95% confidence intervals for the curves in Figure 2 in Table 3. We present the estimates at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years. The cumulative incidence estimates clarify that cumulative incidence increases over time. We changed the results section to reflect this. Results section, Page 10 lines 13-16, Figure 2 and Table 3a and Table 3b.

Line 41 page 8: perhaps restate to indicate exactly what the "event" here is

Response: We corrected this in all sections, the event is loss to follow-up and we defined loss to follow-up in the methods section. Page 5, line 1-3.
Figure 5: perhaps make sure the axis is labeled clearly so that the outcomes measured in those curves are clear. If outcome is LFU which includes mortality but not limited to that, then survival probability is misleading.

Response: We decided to report the cumulative incidence estimates from the competing risks analysis. We report Figure 2-the estimated cumulative incidence curve with mortality, loss to follow-up and death as competing events. We also report Table 3, which has the estimated pointwise cumulative incidence of loss to follow-up, transfer and death at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years. The cumulative incidence estimates are derived from Figure 2. We believe the cumulative incidence curve and accompanying Table 3 for pointwise estimates is a better representation of our findings. We labelled the cumulative incidence curve clearly to show the outcomes as you advised. Page 24, Table 3a and Table 3b, and Figure 2.

Line 51 page 8: Please rephrase "... the hazard ratio of loss to follow up-for children who started treatment... was 5.1..." need to indicate the outcome when stating the hazard ratio. Or another way of stating it is that the hazard or risk of LFU is 5.1 if treatment was initiated between 2013-2015.

Line 56 page 8: similar to above-hazard risk of what?? LFU. This sentence is incomplete-need to state year "2013-2016" and the bracket at end of p=0.0002 also needs to be removed.

Response: we rephrased this sentence to read as follows; “After adjusting for age, baseline CD4, baseline hemoglobin, HIV disclosure status, nutritional status and WHO clinical stage, children who started treatment between 2013 – 2015, had the highest hazard ratio of LTFU, (aHR=5.6; 95% CI:2.2-14.1), compared to those who started treatment between 2003-2005 (Table 4).”

Results section, page 11, lines 16-22.

Line 7, page 9: perhaps to make this clearer, instead of saying "had a shorter time to event" can rephrase to "hazard of loss to follow up was higher among participants without a phone” also, there is an extra bracket on line 9 at start of "survival probability...."

Response: We rephrased this sentence and it now reads as follows: “Compared to children whose care givers owned phones, children without phones were 80% more likely to be LTFU (aHR=1.8; 95% CI: 1.3-2.5).” Results section, page 11 lines 20-23.

-Line 31, page 9: check the footnote to this as in text you state > 5 years and in footnote it’s older than 10 years.

Response: We clarified the age groups categories following your advice in all the tables and sections.

-Line 4, page 12: delete "the" here
Response: We deleted “the” and corrected this error.

Discussion: Would like a little more detail and synthesis of results: Can you go over in more detail what was done to retain children and why only 18% were disclosed their HIV status at baseline?

Response: We worked on the discussion a lot more as advised.

To address the question of what was done to engage patients in care we included the following paragraphs, “In our program, adherence counseling is performed by trained nurse counsellors at each visit. The pharmacists and clinicians also reinforced adherence by performing pill counts and asking specific adherence related questions and addressing any questions that the patients may have. The clinic outreach team also reinforced adherence through a combination of home visits and phone calls aimed at engaging patients in care. In addition, the clinic carries out seminars and workshops and is in touch with community empowerment opportunities and activities that are aimed at creating support networks for families of children living with HIV.” Page 14, lines 3-9.

To address the question of why only 18% were engaged in care, we explained that only children at least 7 years of age or older are routinely disclosed to as recommended by the National SOPs. Our population has a lot of young children as suggested by the median age of 3.8 years. In addition, disclosure to children has been challenging in our setting because most caregivers are not willing to disclose despite the training that we routinely offer to our clients.

We included the following sentence to explain this; “In this sample only 18% of the children knew their HIV status at baseline and these children had better retention in care than those who did not know their HIV status aHR=1.9 (95% CI:1.2-2.9). Disclosure of HIV infection status to a child is an incremental process that starts with partial disclosure to younger children leading to full disclosure for older children [25, 26]. In our study, only children who were at least 7 years old were reported to be fully disclosed. HIV disclosure rates to children in Sub-Saharan Africa remain low, some studies attribute this to health worker and caregiver lack of skills to disclose to children [27, 28]. Training health workers and caregivers in disclosure skills has improved disclosure rates in most places [27, 28].” Page 14, Lines 21-23.

Also, why do you think in that setting the losses to follow up are highest in the 1st 3 months and what specifically would you recommend needs to be done to minimize these losses?

Response: Loss to follow-up is highest before the 3rd month of observation as the slope of the cumulative incidence curve is steepest, which indicates the LUTF is high (See Figure 2). We discussed in the discussion section as follow: “Engagement in care is critical during the early weeks and months after ART initiation. In a case control study from Botswana, it was found that 47.6% (n=51) of the children who were LUTF failed to engage after just one clinic visit as
compared to 1% (n=2) in the control group who engaged in care [4]. The authors suggested that engagement can be improved by addressing personal concerns at the initial and follow-up clinical visits [4]. Other researchers proposed early tracing of patients who missed their appointments [6] and use of risk scores to identify patients at risk of LTFU at baseline and provide individualized risk assessment [17]. Risk scores would definitely be useful in the PCOE clinic. In addition to risk scores, we suggest that dealing with stigma and child disclosure related issues early in the course of treatment and engagement in facility and community treatment support groups would improve engagement in care [18]. ” Discussion page 12, lines 15-23.

For individuals without phones, what other methods can be applied to improve retention into care? Perhaps a little more details in the conclusions and implications of your findings both for implementation and policy.

Response: We added this sentence to explain the methods that our clinic has used to engage patients in care “While access to phones makes contacting patients easier, we recognize that phones are not easily accessible to a lot of families in our setting. Our program has been able to communicate with caregivers who do not own phones through home visits, engaging them in community support groups and allowing them to bring their children to our clinic for other sick and well child visits.” Discussion section, Page 15, lines 8-12.

The conclusion now reads as follows: “LTFU was higher than what is expected in an optimally functioning pediatric HIV treatment program. Among the children LTFU mortality and default were substantially high. Children who started treatment in recent years (2013-2015) had the highest hazard of LTFU. Lack of access to a phone and non-disclosure of HIV-status to the index child was associated with higher hazards of LTFU over the study period. We recommend re-enforcement of client counselling and focused follow up strategies using modern technology such as mobile phones as adjunct to current approaches.” Conclusion section page 16, lines 9-15.

Reviewer 2

Major comments

Definition of loss to follow-up needs further clarification. You state that LTFU was defined as no clinical or pharmacy contact for more than 90 days. But you also mention that some patients only have visits every year. So, was the definition no clinical or pharmacy contact, including home visits and involvement with the outreach team, for more than 90 days?

Response: We rephrased this as follows; “The main outcome was loss to follow-up. Loss to follow-up was defined as no clinical visit and pharmacy contact for at least 90 days after the child missed their last scheduled clinical visit.” Page 5, line 1-3

Yes, there are patients who have been on treatment for a long time who have clinical visits once every year and pharmacy pickups/refills scheduled every 3 months. The clinical visits and
pharmacy refills are scheduled and hence we defined LTFU from the date they missed their scheduled clinical visits and checked if they have been coming for pharmacy refills. We clarified the role of the outreach team in the methods section; page 6, line 18-page 7 line 1-20.

It is difficult to determine when LTFU rate was at its highest. Generally, a hazard function would depict the instantaneous rate of the outcome. I suppose you can also use the KM estimate, but this would be represented by the slope or change in a given period. I recommend you at least state the change in the KM estimate at 3 months. You should also consider presenting the failure KM estimate instead of the survival probability.

Considering your number at risk is halved by 5 years, you should generally only quote estimates up to 5 years, as beyond that the estimates are unreliable.

You need to decide which estimate you want to present - KM probability or cumulative incidence. It well known that the KM probability overestimates in the presence of competing events, which is shown in this study. It would be preferably to just use the cumulative incidence from the competing risks approach.

Response: Thanks for your advice. We decided to use the cumulative incidence from the competing risks analysis. We report Figure 2- the estimated cumulative incidence curve with mortality, loss to follow-up and death as competing events. We also report table 3, which has the estimated pointwise cumulative incidence of loss to follow-up, transfer and death at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years. We understand that the estimates become unreliable after 5 years but we still had 395 children at risk after the 5th year and we included the estimates in our report.

Page 8, last paragraph. You should only be comparing the KM estimate (or cumulative incidence if you choose to) at the 2nd year for those in 2013-2015 vs 2003-2005, as you don't have sufficient follow-up to the 3rd year for those in 2013-2015. Also, you need to explain these findings better; I don't quite understand what you are presenting here. The median time to event isn't available, as your KM estimate doesn't reach 0.5.

Response: We clarified this point as follows: “Children who commenced ART in recent years (2013-2015) had higher cumulative incidence of LTFU [11.5%% (95% CI:6.8-17.4)] after 1 year, compared to those who begun treatment from 2010-2012 [6.2% (95% CI: 3.9-9.4)] and those who begun treatment from 2006-2009 [5.9% (95% CI: 4.1-8.2)] (p<0.0001) during the same period of time (Figure 1, Table 3b).” Results section, page 11, line 7-14.

We only compared during the first year because we did not have enough observation time for those who commenced treatment in 2013-2015.

Page 9, first paragraph: the KM is not an estimate of the time to event, it is the probability that a child will be retained in care. Please revise the results to accurately reflect this, e.g., the
probability of being retained in care was 7% higher in children whose caregivers had a phone compared to children whose caregivers did not have a phone.

Response: As stated in the previous response, we used cumulative incidence estimates from the competing risks cumulative incidence curve. We revised the results and for example we rephrased the section about phone ownership to read as follow: “Lack of access to a phone resulted in higher cumulative incidence of 10.1% (95% CI: 7.1-13.7) compared to those whose caregivers owned phones [4.6% (95% CI: 3.2-6.3)], (p<0.0001).” Results section; page 11, line 11-13.

Your multivariable LTFU model results suggest that children have a greater risk of being LTFU when starting ART in more recent year eras. Is this correct?

Response: Yes, this is what we found. Specifically, the time starting from 2013-2015. This coincides with the implementation of test and treat policy for HIV treatment and option B+. We explored literature and found that a study done in South Africa made similar observations. We discussed this interesting finding in detail on; page 12, line 15-23 (discussion section): “The highest hazard of LTFU was among children who started ART during recent years (2013 -2015). This finding has important programmatic implications because the higher hazard of LTFU occurred in a period when the test and treat policy for children and pregnant women was fully operationalized. The number of children commencing treatment also declined during this period, but likely as a result of reduced infant infections due to successes in prevention of mother to child HIV transmission[16, 20].

In this period all children who were confirmed HIV positive were commenced on ART in contrast to previous years where ART eligibility was based on clinical evaluation and immunological staging [21, 22]. Prior to 2013 ART was only provided to very sick children whose caregivers saw their clinical improvement following ART and associated survival with the treatment, therefore were likely highly motivated to stay on treatment [23]. These findings are similar to those of a study done in South Africa in which children commenced on ART in recent years experienced poorer retention in care [20]. This could be because children commenced on ART in the test and treat era are likely healthier and their care givers may not be motivated to take them for medication pickups and reviews.”

Page 10, second paragraph. In the multivariate model, disclose of HIV status was not significantly associated with LTFU in the model with children aged >7 years. You need to elaborate more in the discussion that age is essentially biased the association. A sentence about how the model only included children >7 years found no association between disclosure and LTFU is needed.

Response; We clarified this point and include the following sentence “In this sample only 18% of the children knew their HIV status at baseline and these children had better retention in care than those who did not know their HIV status aHR=1.9 (95% CI:1.2-2.9). Disclosure of HIV
infection status to a child is an incremental process that starts with partial disclosure to younger children leading to full disclosure for older children [27, 28]. In our study, only children who were at least 7 years old were reported to be fully disclosed. HIV disclosure rates to children in Sub-Saharan Africa remain low, some studies attribute this to health worker and caregiver lack of skills to disclose to children [29, 30]. Training health workers and caregivers in disclosure skills has improved disclosure rates in most places [29, 30].” Page 15, Lines 12 - 20.

You should also present the median follow-up time so readers gain an understanding of how long you followed up your children for.

Response: Median follow-up time is presented as duration on treatment on Table 1. The sentence reads as follow; “The median duration of follow-up was 3.8 years (95% CI: 1.2-6.5) and the median age at baseline was 3.6 years (IQR: 1.3-8.6).” We included this in the results section; page 9 line 11.

In the methods, you need to state what the follow-up period was. What was the 'entry' and 'exit' date for the at-risk period?

Response: We included the following paragraph to explain this detail: “The date of entry into the cohort, which was the start of the follow-up period, was the date the child began taking ARVs as recorded on the medical chart. Children who were transferred out of the clinic and children who died were censored on the date the outcomes were ascertained. All the children who were lost to follow-up were censored 3 months after their last clinic visit. Children who were active in care were censored on December 31st, 2015 when the study was closed. Methods section, page 4 line 15-19.”

Minor comments

Page 5, second paragraph. Results should not be written in the methods section. I suggest you remove the last two sentences.

Response: We removed this paragraph and included it in the results section.

Page 5, third and fourth paragraph. Results should not be presented in the methods section. I suggest you remove the sentence about no model violations and reword the last paragraph to state that a sensitivity analysis where death was considered as a competing event was performed to compare with the estimates not considering death as a competing event.

Response: We reported our results from the competing risks analysis and death was a competing event in the analysis. We decided to leave the sentence about model violations in the methods section because we are describing the analysis we performed and not reporting any results. We believe that the model violations statement would be out of place in the results section.
Figure 2 needs to be properly labelled on the y axis. This is the probability of being retained in care. Similar edits are needed for Figure 5.

Response: We decided to remove the Kaplan Meier analysis and report the findings from the competing risks analysis and this is no longer relevant. We removed the KM curves and now present the cumulative incidence curve (Figure 2).