Author’s response to reviews

Title: Human immunodeficiency virus-associated tuberculosis care in Botswana: evidence from a real-world setting

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Author’s response to reviews:

Reviewer reports:

Rachel Kubiak, MPH (Reviewer 1):

Reviewer 1 comment:

The authors were very responsive to comments and have substantially improved the manuscript.

A few additional comments are below in response to the new manuscript and details of the methods that have become clear through the authors’ response. In particular, given the inclusion of different forms of TB as well as the wide range of times since ART initiation, the authors should consider sub-analyses of the data excluding non-new pulmonary TB cases and also stratifying by time since ART initiation. Alternatively, authors could state the homogeneity of these factors as a limitation in their analysis. Finally, please review all references. I have checked some and there appears to be misalignment.

Response:

Thank you very much for your feedback and input, the reviewer should be commended for having such an impact and substantially contributed to the improvement of this manuscript, for that we are really grateful.

The manuscript has undergone a careful review; the references were reviewed to correct misalignment. Furthermore, we have addressed all the concern raised by the reviewer and provided a response to each comment together with the revised manuscript.
However, while we acknowledge the great contribution of the reviewer, we should also mention that our main objective to conduct this study was to reflect on what is really happening in a real world setting in HIV-associated TB Care, and to assess the implementation of policy and strategies more often developed from evidence from randomized control studies conducted in perfect setting.

Therefore, at the study design we had decided to include all different types of TB and all HIV positive patients regardless of the ART status at TB diagnosis. However, given the difference with regard to etiology and prognosis of different forms of TB, we had created in the analysis variables grouping types of TB having similar prognosis comparing them with other types of TB. The mortality of all the new cases vs. repeat cases (Table 1 and 2), Pulmonary TB vs. extra pulmonary (Table 1 and 2), Smear positive TB vs. Smear negative TB (Table 1 and 2) were compared respectively. Likewise for the time since ART initiation, in analysis we compared mortality of ART naïve at TB diagnosis vs. ART experienced at TB diagnosis (Table 1 and 2 ) and ART use during TB vs. Non ART use during TB (Table 1 and 2 ).

However, to address the reviewer concern, we have stratified mortality rate among ART-experienced patients during TB treatment in 2 groups based on their time of ART initiation. Furthermore, we have added heterogeneity of different forms of TB included in the study and difference in time of ART initiation of ART-experienced patients during TB treatment as a limitation of this study.

Reviewer 1 comment:

ABSTRACT

Line 53: State the difference in survival time.

Response:

Thank you very much for your comment.

The term difference in survival time used here refer to the statistical comparison of survival time using the log Rank test (Mantol-Cox), to show the statistical significance we have included the P value.

Reviewer 1 comment:

Line 55: Says patients more likely to die within two months but in last paragraph of results the authors say more likely to die within three months.
Response:

Thank you very much for your comment.

In the abstract we said only patients with no ART use during TB treatment were more likely to die within the first two months, but in the last paragraph of results we said: The survival curve illustrates that most patients died in the first three months; there were few deaths after three months. However, patients with no ART use during TB treatment were more likely to die within the first two months (Fig. 2). (214 – 217)

Reviewer 1 comment:

BACKGROUND

Line 71-2: Better to state what specific negative impacts are important here (e.g. increased risk of TB and death), and to site a reference.

Response:

Thank you for the observation; we have reworked the paragraph to include the major specific negative impacts. (Line 71-72)

Reviewer 1 comment:

Line 73: Not all references refer to interventions for TB care (e.g. #5). Better to site the international standards of care for TB that you are referring to.

Response:

Thank you for the observation, we have removed all other references and only site the WHO guideline.

Reviewer 1 comment:

Lines 75-79: References needed. This sentence is very long and unclear.

Response:

Thank you very much for the observation, we reworked the paragraph as below to make it more comprehensive for the readers:
“In a patient co-infected with TB and HIV, the two infections potentiate one another. The onset of tuberculosis in HIV-infected patient could result in the worsening of immunological functions with an increased risk of progression from HIV infection to AIDS and death. Moreover, in an HIV high-burden setting, HIV infection has been found to be the most significant risk factor for developing active TB, and also the risk factor of TB reactivation for a person with latent TB.”

Reviewer 1 comment:

Line 80: Should read "…HIV/AIDS patients in sub-Saharan Africa indicates that HIV-associated TB…”
Response:
Corrected, thank you

Reviewer 1 comment:

Line 85: I don't think reference 11, 12, or 13 mention CPT or the effect of CPT on mortality. Reference 14 (a study of CPT in TB regardless of HIV infection, so not HIV-associated TB) found a 29% reduction in death, not 43-45%.
Response:
Thank you for the observation, we have acknowledged the error and we have corrected. The reduction in death found was between 35 % and 46 %, we have put the correct references.

Reviewer 1 comment:

Line 67, 89: This is not stated in reference 2. Suggest removing this reference throughout and using the WHO Global TB Report instead.
Response:
Thank you, corrected.

Reviewer 1 comment:

Line 100: Intensified case finding is not part of what this study was investigating according to the Study Design section so would not mention here.
Response:

Thank you, removed.

Reviewer 1 comment:

METHODS

Line 106: For clarity would say "This was a retrospective cohort study using medical record review to assess the implementation…." Or something along these lines.

Response:

Thank you for the observation; although this was reworked as per the reviewer previous suggestion and comment, we have reworked the sentence as below:

“This was a retrospective cohort study using medical record review to assess the implementation of ART and cotrimoxazole policy, interventions proven to improve the care of adult patients with HIV-associated TB.”

Reviewer 1 comment:

Line 117-8: HIV patients without TB are not a part of this study so not relevant here, nor is IPT

Response:

Thank you very much for the observation. However, this sentence was included to address the second reviewer concern; also we found it important since it will provide the readers context and setting of HIV and TB care in general during the study period.

Reviewer 1 comment:

Line 136: Cluster clinic is a new term for me. Maybe referral clinic is more universally known?

Response:

Thank you very much, both term have the same meaning in this setting, therefore we have replaced cluster by referral.

Reviewer 1 comment:
Line 140: This makes it sound like you pre-determined to include 300 people before beginning the medical record review. Is this the case? If not, would remove this number. Also, what is the difference between someone who is confirmed HIV-positive and someone with a prior HIV diagnosis?

Response:

Thank you for the observation, this was not a pre-determined number therefore we have removed the number.

Furthermore, there is no difference between someone who is confirmed HIV-positive and someone with a prior HIV diagnosis since both of them have HIV; this sentence was reworked based on the reviewer previous concern. However, we have removed prior HIV diagnosis since both have a same meaning.

Reviewer 1 comment:

Lines 144-146: New, repeat, meningitis, and bone TB are quite different in terms of etiology and prognosis. It would be interesting to know if their care was different (e.g. if time from ART initiation differs) and it is important to separate out these types of TB in the Results. Small numbers will probably prevent analyses of some, but perhaps you could look at KM curves and HRs for new PTB cases.

Response:

Thank you for the observation, we only had few cases of TB meningitis and bone TB, hence not allowing us to conduct any statistical analysis.

However, given the difference with regard to etiology and prognosis of different forms of TB, we had created in the analysis variables grouping types of TB having similar prognosis comparing them with other types of TB. The mortality of all the new cases vs. repeat cases (Table 1 and 2), Pulmonary TB vs. extra pulmonary (Table 1 and 2), Smear positive TB vs. Smear negative TB (Table 1 and 2) were compared respectively. Likewise for the time since ART initiation, in analysis we compared mortality of ART naïve at TB diagnosis vs. ART experienced at TB diagnosis (Table 1 and 2 ) and ART use during TB vs. Non ART use during TB (Table 1 and 2 ).

However, to address the reviewer concern, we have stratified mortality rate in 2 groups based on their time of ART initiation. Furthermore, we have added heterogeneity of different types of TB included in the study and difference in time of ART initiation as a limitation of this study.
Reviewer 1 comment:

Lines 148-152: It is confusing to have two different definitions of "ART experienced patients." Choose one.

Response:

Thank you, done.

Reviewer 1 comment:

Line 170: In the author's response, they say that ART use during TB treatment, major side-effects, and opportunistic infections were included in the Cox models as time-updated covariates, but this is not mentioned here.

Response:

Thank you, included.

Reviewer 1 comment:

Throughout, choose 0 or 1 decimal points and be consistent (e.g. lines 185-187 have results with 0, 1, and 2 decimals).

Response:

Thank you, corrected.

Reviewer 1 comment:

Line 184: Related to line 140, why were 88 TB-HIV patients not included?

Response:

Thank you for the observation, the reason for exclusion of 88 TB-HIV patients were included in the first manuscript and then removed on the revised manuscript as per the reviewer suggestion and concern. However, 88 patients (23%) were excluded, as their medical records were missing or not captured. We have included this sentence in the revised (2) manuscript.
There were 30 deaths among ART-experienced patients, which includes 86 who initiated ART within 3 months prior to their TB diagnosis, 40 initiated ART within 4 weeks following TB diagnosis, and the remainder initiated TB a median of 37 months prior. If my understanding is correct, these seem like very different populations and it would be helpful to separate mortality findings by two groups (recent and non-recent) or all 3 groups.

Response:

Thank you very much, we have stratified mortality rate as per the reviewer suggestion.

Reviewer 1 comment:

Line 199: In Table 1, 1% (not 2%) of survivors are smokers

Response:

Thank you, corrected.

Reviewer 1 comment:

Line 201: add p-value for opportunistic infection.
Line 205: Table 2 has p-value for OI at <0.001.

Response:

Thank you, corrected.

Reviewer 1 comment:

Line 210-212: This would fit better in the paragraph about ART (lines 188-193).

Response:

Thank you, done.

Reviewer 1 comment:

DISCUSSION
Is there any data on ART adherence or only initiation? If the latter, please state as a limitation. If you have data on adherence, please include in Table 2 analyses.

Response:

Thank you very much for the observation, unfortunately we only had few data on ART adherence hence we did not report it since too much data were missing. We have stated it as a limitation.

Reviewer 1 comment:

Line 219: …mortality is still high in Botswana, or in the 2 districts.

Response:

Thank you very much for the observation.

Although this study was conducted in these districts in Botswana, as the districts are similar to other districts with regard to HIV-associated TB epidemiology, the results can be generalised to the country as a whole.

Reviewer 1 comment:

Line 220: You did not show in increase in CPT because there is no mention of what it was before the study period, or of uptake over time. Instead we see that uptake was comprehensive during the study period.

Response:

Thank you very much for the observation, to address the reviewer concern we have reworked the sentence as follow:

‘‘There is a substantial success in the implementation of Cotrimoxazole preventive therapy with an uptake of 100 %,’’

Reviewer 1 comment:

Line 229, 279: The meaning of "baseline" in the context of other studies is not clear, perhaps ART initiation?

Response:
Thank you for the observation, in line 229, the baseline screening of TB is in the context of ART services entry, therefore baseline refer to pre-ART screening of TB as it is recommended in the care of HIV.

In line 279, the baseline screening of other opportunistic infection refer to the assessment of co-morbidities at HIV-associated TB diagnosis, this promote patient centered care, since more often clinicians are more focus on treating the disease than providing a comprehensive and holistic care to the patient.

Reviewer 1 comment:
Lines 250-252, 279-282: Bold statements that are not fully supported with the findings from this study. They are reasonable in the context of the literature, but the authors should be explicit that these statements are based on the literature and/or guidelines.

Response:
Thank you for the observation, we strongly agree with the reviewer and this could be shown by the language that we have used in discussing our findings in the context of existing body of knowledge, we are not fully supporting those statements by our findings but making some observation based on the existing body of knowledge and the trend that we have observed in our findings. This is very important since it could provide more information to the readers on the HIV-associated TB care in the context of existing evidence.

Reviewer 1 comment:
Line 271: Should read "…HIV-associated TB patients in Botswana…” (add in "TB").

Response:
Thank you, this was a typing error.

Reviewer 1 comment:
Line 284: Should read "…implementation of CPT, there is still…” (not "…implementation of Contrimoxazole preventative there is still…”).

Response:
Thank you
Reviewer 1 comment:

Lines 298-300: This sentence seems fragmented and should be clarified.

Response:

Thank you, we have reworked the sentence to address the reviewer concern and add other limitations as suggested by the reviewers.

Reviewer 1 comment:

TABLES 1, 2

- Order variables in the same way.
- List like variables together (e.g. No ART use during TB treatment and ART naïve).

Response:

Thank you, done.

Reviewer 1 comment:

TABLE 2

- Authors state all variable in univariate analysis with p-value <=0.1 will be included in the multivariable analysis, but in the table smoking has p=0.130 and is included in multivariable analysis while smear positive PTB (p=0.028), loss of weight (p=0.032), and CD4<200 (p=0.046) are not. An explanation or correction is needed.

Response:

We have used the Forward Stepwise (Likelihood Ratio) method. The variables entered at each step were Body weight, ART use during TB, weight loss, smear positive PTB, major side effect, CD4 count < 200, Opportunistic infection, age group, and Hb < 10 as they met the criteria for inclusion in the multivariate analyses. In the table we have just shown the variables which remained in the final multivariate equation (model).

Reviewer 1 comment:

FIGURE 2
- X-axis should have a clearer axis title (e.g. Follow-up time (months)) and no decimals because it tick marks are given in 5 whole unit increments so specifying 5.00, 10.00 etc is not informative and clutters the axis.

Response:

Thank you very much for the observation, however, this figure is an output from SPSS as a picture with its own headings, we have tried our best but we were unable to modify it.

Furthermore, we should mention that the interpretation of this figure has helped us in understanding of mortality and survival trend of HIV-associated TB patients on ART and not on ART during TB treatment in this setting.

Reviewer 1 comment:

- Ideally this figure would distinguish between forms of TB or show only new PTB cases.

Response:

Thank you very much for the observation,

However, we should mention our main objective in this study was to assess in a real-world setting the survival of patients on treatment for HIV-associated TB and the implementation by healthcare providers of ART and CPT policy. Given that every HIV-associated TB patient included in the study received CPT, therefore we were unable to do any survival curve with CPT as exposure. But since ART uptake during TB in this study was 84 %, we had then decided to study survival and mortality in HIV-associated TB patients on ART and not on ART during TB treatment in this setting, so we can be able to answer to the research question.

Furthermore, we only had few cases of TB meningitis and bone TB, hence not allowing us to conduct any statistical analysis.

Patrick Cudahy (Reviewer 2):

Reviewer 2 comment:

The addition of a cox proportional-hazards model has significantly strengthened this analysis. The manuscript identifies several areas where healthcare delivery could be strengthened, highlighting the benefit of this programatic data.

Response:
Thank you very much for the feedback, we are also grateful for your input and remarks which made a difference.

Reviewer comment:

One area that does still require revision is that without CD4 data, the conclusion that ART naive patients were inappropriately not commenced on therapy is not supported. Most deaths were before two months, which is before ART should have been started in those with CD4 >50 per WHO guidelines, of CD4 > 100 per Botswana guidelines. During the time period of this study, persons with HIV with higher CD4 counts (>350) without a TB diagnosis were more likely to not have been started on ART, so the ART naive group may have had high CD4 counts. In addition, the Cox PH analysis showed that another significant predictor of death was major side effects (as defined as "requiring first-line TB treatment to be discontinued") which would have also appropriately delayed ART initiation. Based on existing evidence, CD4 count and timing of ART are both very important in the survival benefit. Since you do not have the CD4 data, the conclusions you can draw about this are weaker than what you state.

Response:

Thank you very much for the observation, we strongly agree with the reviewer that based on the existing evidence, CD4 count and timing of ART are both very important in the survival benefit, that is why as so much data were missing we have included lack of stratification of CD4 count and timing survival analysis as one of the limitation of this study.

However, the Botswana guideline during the study period was as follows: Patients with a CD4 count ≤100 cells/mm3 ART were to be started as soon as they were tolerating TB Treatment and patients with CD4 count >100 cells/mm3 were to be started within 8 weeks and at least by the end of the initial phase of TB treatment. No patient was supposed to complete TB treatment without being initiated on ART.

Among HIV-associated TB patients who were ART naïve at TB diagnosis included in this study, there were 65 (65/83; 78%) survivors (Table 1). Of these 28 (28/65; 43%) (Table 1) were not commenced on ART during TB treatment, completed their TB treatment without being initiated on ART. This was against the Botswana guideline recommendation therefore it is supporting our conclusion that ART naive patients were probably inappropriately not commenced on therapy. Furthermore, in the final cox proportional-hazards model the lack of ART use during TB treatment was significantly associated with higher mortality. But our findings were limited with regard to CD4 strata and the timing survival analysis benefit because of lack of stratification of CD4 count. Therefore, the lack of stratification of CD4 count was included as one of the limitation of this study.
Reviewer comment:
In your reply to my prior comments you state that "we should also note that both integration of ART into TB treatment and timing of ART initiation during TB treatment have been shown to improve survival among HIV-associated TB patients". I do not know what the distinction is. I am not aware of studies that have looked at concurrent initiation of both TB and HIV therapy at the same time.

Response:
Thank you for the observation, in our previous reply our statement of both integration of ART into TB treatment and timing of ART initiation in survival benefit was referring to some randomized control studies which looked at HIV-associated TB patients to start antiretroviral therapy either during TB treatment (in two integrated-therapy groups) or after the completion of TB treatment (in one sequential-therapy group), and concluded that The initiation and integration of antiretroviral therapy during tuberculosis therapy significantly improved survival. (Abdool Karim, Salim S., et al. "Timing of initiation of antiretroviral drugs during tuberculosis therapy." New England Journal of Medicine 362.8 (2010): 697-706.).


Reviewer comment:
I also would suggest not reporting mean survival times (lines 208-210) since most patients were only followed for 6 months and the cases with bone or CNS disease that were followed longer would bias this. In general, median survival is better to report but when I look at the Kaplan-Meier curves, the survival function is never less than or equal to 0.5 for either group, so there is no median survival. I would omit these summary statistics, but keep the kaplan-meier figure.

Response:
Thank you for the observation, we have removed those summary statistics.