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:

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TO: Sheela Shenoi
Editor-in-Chief
BMC
Dear Dr Sheela Shenoi,

I am pleased to resubmit the revised manuscript an original research article entitled ‘Human immunodeficiency virus-associated tuberculosis care in Botswana: evidence from a real-world setting” by Jacques L. Tamuzi, Esperance Manwana and Ley M. Muyaya for consideration for publication in BMC infectious diseases.

We thank you very much for the feedback and the suggestions, we are really grateful for you helping us to improve our manuscript. The manuscript has undergone a careful extensive editing based on the observation and suggestions made by reviewers; all key issues were addressed, we have provided a specific response to each comment and a revised manuscript as well.

Furthermore, we have conducted as suggested by both reviewers a Cox proportional hazard regression to adjust for baseline severity and indentify predictors of mortality. But CD4 count was not stratified among ART naïve patients to analyze the relation with timing of ART initiation and mortality as so much data were missing. Hence, we have limited our analysis to assess the benefit of integration of ART into TB treatment.

Although, the data presented in this study were for 2013, we have done our best to see if there was any change with the current trend of all key issues presented in this study in the district (2018) report, the WHO TB global (2018) report for Botswana. Therefore, we strongly believe this manuscript will provide programmatic insights of HIV-associated care in Botswana, to health care providers and policy makers; this will probably contribute to their efforts in helping the country to achieve the 90-90-90 targets.

Thank you very much for consideration.

Sincerely,

Dr Ley Muyaya Muyaya
Reviewer reports:

Rachel Kubiak (Reviewer 1):

Comment:

This is a retrospective cohort study using data abstracted from clinic medical records in one district in Botswana. The analytical cohort is comprised of all newly diagnosed TB patients in 2013 with documented HIV status and complete medical records. The authors aimed to describe treatment characteristics in their cohort and the relationship of ART with death over a 12 or more month follow-up period.

The authors created an important dataset that yields valuable programmatic insights on the implementation of national policies at the local level. The paper could be strengthened with a more detailed and focused introduction; clarification of the methods and defining key terms (e.g., HIV-associated TB, ART experienced, TB case, ART uptake, unexplained anemia); and focusing the conclusions on implementation of comprehensive treatment for HIV-TB co-infected adults in the study setting. With these changes, this manuscript will add to the literature with important insights on the success of implementing national policies at a local level.

Response:

Thank you very much for the feedback and the suggestions, we are really grateful for you helping us to improve our manuscript. The manuscript has undergone a careful extensive editing based on the observation and suggestions made; all key issues were addressed, below we have provided a specific response to each comment and a revised manuscript as well.

SPECIFIC COMMENTS

INTRODUCTION

Lines 70-72:

It would be helpful to make this paragraph more specific to the goals of this research paper, for example by listing the relevant negative impacts of HIV on TB control, and relevant interventions (presumably ART, cotrimoxazole).

Response:

We have made the paragraph more specific to our goal as suggested by the reviewer, and we have acknowledged that this will be very useful for the readers.
This analysis does not include people with LTBI, so it is a distraction to include LTBI care in the introduction and should be removed.

Response:

Thank you, removed.

What "clear policy and specific interventions" are you referring to? For your readers not familiar with the relevant HIV and TB treatment guidelines in Botswana during the study period, it would be informative to detail these, including CPT administration.

Response:

We have reworked the paragraph and included this as below:

In view of this poor prognosis in patients with HIV-associated TB, in 2012 prior the study period, Botswana had adopted the revised WHO (2010) guidelines which recommend that all patients with HIV-associated TB should be initiated on ART regardless of CD4 count, also the use of cotrimoxazole preventive therapy (CPT) and the intensified TB case finding among people living with HIV.

METHODS

Please include that this is a retrospective medical record review here to give context to the reader.

Response:

Thank you, included

Since pediatric LTBI is not part of your analysis, it is not relevant to the methods and can be removed.
Response:

Thank you, removed.

Line 113:

Later, in the results it seems your study population is adult TB patients initiating treatment in 2013 who also tested positive for HIV at the time of their TB diagnosis or had a confirmed prior HIV diagnosis. Here it's written as HIV-positive patients who were diagnosed with incident TB in 2013. Can you please clarify who the study population is by clarifying your criteria for inclusion? Also, if 300 is the number of people who met your criteria, then state 300 only in the results. If 300 is the maximum sample size you chose to have, then please state that explicitly.

Response:

Thank you for this, we have reworked the sentences as below to make the inclusion criteria clear:

“Between 1 January 2013 and 31 December 2013, 300 confirmed18 HIV-positive patients or had a prior HIV diagnosis aged ≥ 15 years with a confirmed TB diagnosis by either laboratory or X-ray and medical records available were included in the analysis”.

We would also want to note that based on WHO age classification for Tuberculosis disease, age 15 and above is considered as adult.

Line 114:

Please explicitly state what laboratory tests could lead to a TB diagnosis in your study.

Response:

We added a paragraph describing the laboratory tests that could lead to a TB diagnosis in the study as below :

“Generally, during the study period available investigations for TB included smear microscopy, chest radiology, abdominal ultrasonography, and fine-needle aspiration of lymph nodes for acid fast bacilli microscopy, which were done at primary and district hospital laboratories. Whilst culture and drugs sensitivity were only done at the National health laboratory but not on routine basis”.

Lines 115-119:
This is helpful information on data collection but should be removed because it is repeated in the Data Collection section where it is better suited.

Response:
Thank you, removed.

Line 121:
"Primary outcome" indicates one, but three are listed. Please clarify if there was one primary outcome or three outcomes of interest.

Response:
The primary outcome was mortality; we have reworked the paragraph as below to address the reviewer concern and the issue of follow up time period:

The primary outcome was mortality, defined as any death that happened during TB treatment, which ranged from 6 months in new TB cases, 8 months in repeat TB cases, 12 months in TB meningitis cases and up to 18 months in bone TB cases.

We defined ART uptake among HIV-associated TB patients during TB treatment as the commencement of ART during TB treatment or patients had been on ART prior TB diagnosis. ART experienced patients were defined as HIV-associated TB patients who had been on ART prior TB diagnosis. Additionally, Major side effects were defined as any side effect that happened during TB treatment requiring first-line TB treatment to be discontinued.

Furthermore, we defined unexplained anemia as anemia with Hb < 10 g/dl with no anemia etiology discovered after a comprehensive evaluation of the patient, and finally the Cotrimoxazole uptake among HIV-associated TB patients was defined as the administration of Cotrimoxazole preventive therapy during TB treatment.

Line 126:
States data was abstracted over the duration of TB treatment (~6 months) but Figure 2 shows people out to ~17 months. Were there MDR-TB cases? Please clarify here how long treatment can be expected to last in this cohort, or if you included time past TB treatment completion, what criteria were used to determine duration.

Response:
Thank you for the observation, during the study period, the duration of TB treatment based on the Botswana guideline, varied from 6 months in new TB cases, 8 months in repeat TB cases, 12 months in TB meningitis cases. TB of bones like spine the treatment could be extended up to 18 months since the standard treatment monitoring doesn’t apply to this category of patients; rely mostly on clinical judgment and protocol (SOP) of the hospital.

In addition, during the treatment of TB, there can be treatment interruption due to major side effect (ex: hepatotoxicity…) or patients related reasons (ex: defaulter), in such case the guideline advice to prolong the duration of TB treatment to compensate for missing doses. In addition, there was also a poor compliance to the treatment duration which was observed in some cases as well.

MDR-TB cases also were not included in this study since they did meet the inclusion criteria.

Line 127:
Was death also ascertained using medical records?
Response:
The death was ascertained using the Botswana regional civil registration system, which is closely working with the hospital record department.

Line 128:
Unclear what "HIV-associated patients" means.
Response:
It is typing error: HIV-associated TB patients, corrected

Line 129:
Chi-square does not have an 's' at the end.
Response:
Corrected
Line 130:
Why not use the T-test to compare means?
Response:
Thank you for the observation, it was indeed T-test which was used, this was a typing error.

Line 131:
Kaplan-Meier curves are useful for this purpose. Please also calculate the median (interquartile range) time to death and hazard ratio.
Response:

RESULTS

Line 147:
Please write out SD the first time this abbreviation is used. Range and peak are unnecessary.
Response:
Thank you, corrected.

Line 151:
The term "ART-experienced" is unclear. Please define and use consistently throughout (e.g. different, clearer terms are used in figure 1).
Response:
Thank you for the observation, to address the reviewer concern; we have clarified the term ART–experienced by defining it under the method. We have defined ART experienced patients at the time of TB diagnosis as HIV-associated TB patients who had been on ART prior TB diagnosis. While ART experienced patients during TB treatment were defined as HIV-associated TB patients who had been commenced on ART during TB treatment or had been on ART prior TB diagnosis.

Furthermore, the burden of HIV-associated TB in ART programme in Sub-Saharan Africa has been classified in 3 groups of patients, for which different interventions could be required to
reduce mortality. These include: 1) those who first present to health services with TB and are diagnose with HIV through routine HIV testing, 2) HIV-infected patients enrolling in ART services who are found to have active TB during baseline screening. 3) HIV-infected patients already enrolled on ART who develop TB during ART.

In addition it has been found that in the first few months following ART initiation, much of the HIV-associated TB burden is due to ‘unmasking’ of asymptomatic or minimally symptomatic disease that was present at baseline but missed during screening. Therefore, in Figure 1, we wanted to show the burden of HIV-associated TB in this setting, based on the above classification; this could guide policy and care.

Line 152-3:

Would be clearer to combine these sentences and use the same denominator for both percentages (e.g. 86 (40%) had TB within three months of ART initiation and 83 (38%) were ART-naïve…. (Fig 1.)). Alternatively, clarify the denominator for the 83 (given as 28%).

Response:

The purpose of this section as we previously mentioned is to show the burden of HIV-associated TB based on the above classification, at our knowledge this is the first study in Botswana to provide such classification, this could help to have targeted intervention in different category of patients in ART programme to address the burden of TB in this setting.

Of the 300 patients included in the analysis, we have divided them in two groups of patients based on their ART status at the time of TB diagnosis, 217 (72 %) were ART experienced at TB diagnosis and 83 (28 %) were ART-naïve at TB diagnosis.

Line 155:

You had previously used a different term for ATT. Please be consistent.

Response:

Thank you, corrected.

Line 155:

Give n for overall number starting ART.
Response:

Thank you, done.

Lines 157-159:

Denominator unclear for these percentages and I'm not sure is appropriate. Best to indicate of those on ART, X% died versus Y% of those not on ART (assuming that's what is meant by ART-experienced means).

Response:

Thank you for the observation, we have corrected the denominator and put in bracket the numerator and denominator used to make it clear to the reader.

Line 159, 162, 163-6:

Rounding up to a whole number for percentages is appropriate.

Response:

Thank you, done.

Line 162:

Give mean age of those who died versus did not die.

Response:

Thank you for the observation; however, for Cox-analyses purpose for all continuous variables, we have used stratification to have binary variables and reference group for easy clinical interpretation. We have only given the mean age for the overall group of patients included in the study.

Line 163:

Define "unexplained anemia" in the methods. Write out hb the first time it is used.
Response:

Thank you, done.

Line 173:
Please specify the gaps you identified. Presumably ART initiation/adherence since CPT was excellent.

Response:

Thank you for the observation, to address the reviewer concern, we reworked the paragraph as follows:

“Our study shows that the burden of HIV-associated TB and related mortality is still high. There is a substantial increase of implementation of Cotrimoxazole preventive therapy with an uptake of 100%, however there are still gaps in the implementation of ART policy for HIV-associated TB patients despite the national policies, strategies and guidelines.”

Line 178:

"Significant" is a statistical term and should not be used in this way.

Response:

Thank you, corrected.

Line 179:

"Incidence" is a rate of new cases over time, which I don't believe is reported here, nor is prior IPT use reported in this population so I don't think this conclusion is warranted. The focus of this paper is on the ART use and its relationship with death so conclusion should focus on this.

Response:

It is true that the incidence rate was not reported in this study, but we have shown in the study that there was 551 patients registered for TB in 2013 in Serowe/Palapye district, only 163 were HIV negative, of the 300 with HIV-associated TB included in the study, 217 had been on ART prior to TB diagnosis. Furthermore, we have indicated that despite the WHO recommendation and overwhelming evidence about treatment of Latent TB in high risk people, IPT use was not recommended for adults during the study period and also up to date, yet the trend of TB disease
in Botswana is indicating that the proportion of patients developing TB is higher in HIV patients already on ART compared to ART naïve and the general population.

Although the study was mainly focus on ART and CPT policy, following the analyses of data in local and context setting, we found that there were some interventions to suggest which could help to address the burden of HIV-associated mortality and morbidity in this setting.

However, to address the reviewer concern we have reworked the paragraph as follows:

“In this cohort of HIV-associated TB patients, of the 217 (72%) patients who were ART-experienced at the time of TB diagnosis, 60% patients had been on ART for more than 3 months at the time of their TB diagnosis, with median time from ART initiation to TB diagnosis of 37.15 months (interquartile range [IQR]: 13.93-75.97). Our finding suggest that further interventions to prevent TB among people living with HIV, such as IPT and intensified case finding, are warranted in this setting. Moreover, studies conducted in Brazil and South Africa report that whereas IPT and ART were both effective in reducing TB risk among adult people living with HIV, the combination of the two interventions was more protective than either alone, resulting in an 80% and 89%, respectively, reduction in TB rates when compared to patients receiving neither intervention.

Line 203:
This number (48%) is not mentioned in the results. It should be included there.

Response:
Thank you, included.

Line 212:
Similar proportion died or were on ART and CPT in Malawi and Swaziland?

Response:
Thank you for the observation, it was a similar proportion of those who died and with almost the same uptake of ART and CPT. However, to address the reviewer concern, we have reworked the sentence by including a similar proportion of mortality.
Do you have information on the % with cryptococcal disease, cytomegalovirus, or bacterial infections that could also be included in the results?

Response:

We would have loved to include the details regarding the above opportunistic infection but unfortunately we don’t have all the information.

Line 223:

Given 84% on ART and 100% CPT, "little implementation of national policies" seems unnecessarily harsh. Please specify which "findings of this study" you are referring to. Your recommendations can then reflect your specific findings.

Response:

TABLE

1 - Better to give mean (SD) age than categories, or justify these

Categories

Response:

We wanted to see the distribution and comparison of mortality and survivors among age categories to see which age category is the most affected one, than to just give the mean age. Furthermore, it has been shown older people (60 years and above) are a high risk group for TB, with poor outcomes. In addition, for Cox-analyses purpose for all continuous variables, we have used stratification to have binary variables and reference group for easy clinical interpretation.

We have only given the mean age for the overall group of patients included in the study in the main results text.

Comment:

- What is the denominator for ART-naïve percentages? It is not the column total.

Response:

It is the column total, corrected.
Comment:
- Footnote d: missing data for a range of participants?

Response:
There were some variables (Fever, Cough, Night sweat, loss of weight) which were having almost the same number of missing data with number ranging between 21 to 25 participants for each variable; therefore to avoid having a congested footnote, we had decided to have one letter symbol and a range of participants for these variables.

Comment:
- Be consistent with showing 0 or 1 decimal for %s

Response:
Thank you, corrected.

Comment:
FIGURE 1
- No key or additional title within figure is necessary

Response:
Thank you, removed.

Comment:
- One group should be >=3 or =<3 unless those with exactly 3 months of ART were excluded

Response:
Thank you, it was a typing error that we have corrected.

Comment:
FIGURE 2
Labels and heading should be more informative and full words

Response:
The figure is an output from SPSS with its own headings; but the figure legend is more informative.

Comment:
- No decimals needed for follow-up time

Response:
The follow up time is expressed in months, it is the cumulative survival which having decimals.

Comment:
Unclear why follow-up time longer for one group or why it goes up to ~18 months when it depicts those on TB treatment. Are MDR-TB patients included in these analyses?

Response:
Thank you for the observation, during the study period, the duration of TB treatment based on the Botswana guideline, varied from 6 months in new TB cases, 8 months in repeat TB cases, 12 months in TB meningitis cases. TB of bones like spine the treatment could be extended up to 18 months since the standard treatment monitoring doesn’t apply to this category of patients; rely mostly on clinical judgment and protocol (SOP) of the hospital.

In addition, during the treatment of TB, there can be treatment interruption due to major side effects (eg: hepatoxicity…) or patients related reasons (eg: defaulter), in such case the guideline advice to prolong the duration of TB treatment to compensate for missing doses. In addition, there was also a poor compliance to the treatment duration which was observed in some cases as well.

MDR-TB cases also were not included in this study since they did meet the inclusion criteria.

Additionally, we should mention that 300 patients were included in the study and followed during TB treatment equally, this survival analysis was just conducted to show the survival time between patients on ART VS. Not on ART, the difference in follow time might be because those Not on ART had completed their TB treatment based on their category earlier than those on ART or had died. In addition, of the 300 included in the study, only 43 patients were not commenced on ART during TB treatment.
Patrick Cudahy
(Reviewer 2): "Human immunodeficiency virus-associated tuberculosis care in Botswana: evidence versus real-world setting" is a retrospective analysis of programmatic data to evaluate mortality while on antitubercular therapy in HIV and TB co-infected patients in a resource-limited, high-burden setting. It is commendable that the authors have assembled a relatively complete picture of HIV/TB outcomes from this setting, even if the data is a bit old. It also has a good summary of baseline predictors of mortality but this needs to be adjusted for multiple analysis or extended to a logistic regression. Some time to event analysis is performed, but the stratification of groups is problematic and needs to be rethought. It is a missed opportunity that a more sophisticated analysis like a Cox proportional-hazards model is not used. The conclusions also need to better fit the data presented.

Response:
Thank you very much for the feedback and the suggestions, we are really grateful for you helping us to improve our manuscript. The manuscript has undergone a careful extensive editing based on the observation and suggestions made; all key issues were addressed, below we have provided a specific response to each comment and a revised manuscript as well.

Specific comments are as follows-

Title: This article does present evidence, so perhaps "Human immunodeficiency virus-associated tuberculosis care in Botswana: evidence from a real-world setting" is better

Response:
Thank you for the suggestion, we have accepted the reformulation of the title as suggested.

Abstract:
Line 38: "the implementation of specific interventions", What interventions? No interventions are mentioned in the methods. Please be more specific

Response:
It is the implementation of Antiretroviral therapy and Cotrimoxazole preventive therapy policy, we have reworked the abstract, background and methods to be more specific.
Background:

Line 73: When was universal ART introduced in Botswana? What was the ART policy at the time of this study (2013)? Was IPT and cotrimoxazole part of the Botswanan guidelines at the time of this study?

Response:

The universal ART was introduced in 2001 in Botswana. In 2012 prior the study period, Botswana had adopted the revised WHO (2010) guidelines which recommend that all patients with HIV-associated TB should be initiated on ART regardless of CD4 count, also the use of cotrimoxazole preventive therapy (CPT) and the intensified TB case finding among people living with HIV.

IPT use was not recommended for adults during the study period and also up to date.

To address the reviewer concern, we have reworked the background and methods to include these details.

Comment:

What about changes in diagnostics for TB that are more sensitive in HIV/TB coinfection? Was geneXpert in use during this time?

Response:

The Gene Xpert greatly increased case finding compared to smear microscopy, rapid TB diagnosis and detection of rifampicin resistance. But the test was not part of the guideline during the study period, has been introduced since 2016 in Botswana.

Generally, during the study period available investigations for TB included smear microscopy, chest radiology, abdominal ultrasonography, and fine-needle aspiration of lymph nodes for acid fast bacilli microscopy, which were done at primary and district hospital laboratories. Whist culture and drugs sensitivity were only done at the National health laboratory but not on routine basis.

Furthermore, to address the reviewer concern, we have reworked the methods and discussion to include these details.

Line 92: "the implementation by policy makers and healthcare providers of specific interventions that are proven to benefit patients" Again, be more specific about what interventions were recommended in this setting at this time.
This dataset is relatively old, so there needs to be more context about the diagnostics and therapies that were standard at the time.

Response:
Thank you for the observation, we have reworked the background and methods to be more specific and give the context of diagnostics and therapies during the study period.

Methods:
Line 96: Which interventions?
The implementation of ART and CPT policy, we have reworked the methods by including this.

Line 103:
What was the ART policy for those without TB?
Response:
For those HIV patients without TB, they were eligible for ART if CD4 count < 350 or WHO clinical stage 3 or 4.
We have reworked the methods section to include this.

Line 104:
Would simplify to say that "IPT was not recommended for adults."
Response:
Thank you, corrected.

Line 109:
"the mother's clinic" Is this the pre-natal clinic? I'm not familiar with the term
Response:
In the structure of public health system in Botswana, mother clinic means a referral clinic or main clinic or cluster clinic.
However, to address the reviewer concern, we have removed the term mother clinic to replace it by cluster clinic.

Line 109:

ART only available in hospitals?

On line 107 it says that TB and HIV services are co-localized at the "primary healthcare level" which I took to mean clinics. Does that mean non-ART HIV services? This paragraph is confusing.

Response:

The HIV services comprised of Routine HIV testing, HIV Counseling, ART drugs dispensing, ART adherence counseling and ART prescription. In addition, the primary healthcare level comprised of cluster’s clinics and health posts.

While others HIV related services were provided at the health posts, cluster’s clinic and hospital, the prescription of ART was only done at the cluster’s clinic and the hospital.

To address the reviewer concern, we have reworked the paragraph to specify that the prescription of ART was only done at the cluster’s clinic and the hospital.

Line 113:

Would emphasize that these were all of the HIV/TB co-infected patients with an available medical record and not a sample of a larger group.

Response:

We were describing the inclusion criteria that we have used to come up with this sample. However, of the 388 HIV-associated TB patients who were registered in 2013 in Serowe/Palapye District, 300 were included in the study.

Line 114:

"Laboratory" Please be more specific. I assume smear, culture, and/or Xpert.

Were these all pulmonary TB or were there extrapulmonary? Did they all get drug-susceptibility testing? Did any have MDR or XDR?
Generally, during the study period available investigations for TB included smear microscopy, chest radiology, abdominal ultrasonography, and fine-needle aspiration of lymph nodes for acid fast bacilli microscopy, which were done at primary and district hospital laboratories. Whist culture and drugs sensitivity were only done at the National health laboratory but not on routine basis. Furthermore, MDR or XDR were not included in the study.

We have included these details in the methods.

Line 121:
The outcome is mortality. Initiation of ART and CPT are some of the predictors.

Response:
Thank you, corrected.

Line 133:
You say they were censored "during the study period", so if they started TB treatment on December 15th, they were censored on January 1st? It would seem to make more sense to censor after their last clinic visit while on TB treatment.

Response:
Thank you, corrected.

Results:
Line 152: What ART regimen were they on?

Response:
The standard ART first-line regimen for TB patients was: tenofovir (TDF) + emtricitabine (FTC) or Lamivudine (3TC) + efavirenz (EFV). Nevirapine (NVP) was used in cases of EFV intolerance. The standard ART second-line regimen was zidovudine (AZT) + lamivudine (3TC) and double dosed LPV/r (ritonavir-boosted lopinavir).
International recommendations are that those with CD4 < 50 be started on ART within 2 weeks and those with CD4 > 50 within 8 weeks. Please present the statistics to show what % with CD4 <50 and not on ART were started within 2 weeks (along with the mean time to starting ART), and what % of those with CD4 >50 and not on ART were started within 8 weeks (with mean time to start)

Response:

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.

Of the 300 patients included in the study only 83 were ART naïve at the time of their TB diagnosis, the remaining (217) patients had been on ART prior TB diagnosis. Furthermore, we should mention that this study was conducted in a resource limited setting; of the 83 HIV-associated TB patients who were ART naïve at the time of their TB diagnosis most of them did not have a baseline CD4 count done, this could have been because of frequent break down of machine or lack of reagent. Hence, we had much missing data, for this reason we were not able to do stratification per CD4 count level to see if the guideline was followed with regard to the timing of ART initiation by clinician or not.

However, the Botswana guideline during the study period was recommending the ART initiation as soon as the patient is tolerating TB treatment for those with severe disease or by the end of initial phase for stable patient.

Were they all given the same TB regimen? What was it?

Response:

The standard first-line TB treatment during the study period was rifampicin, pyrazinamide, ethambutol and isoniazid during the two initial months (‘intensive phase’), followed by rifampicin, isoniazid and ethambutol for the next four months (‘continuation phase’). While, in patients with central nervous system diseases or TB infection in their bones, the continuation phase was extended to 12 months, in repeat TB cases the intensive was extended for one month with streptomycin included for the first two months and the continuation phase was extended to 5 months.

We have included these details in the methods.
Opportunistic infections (unless diagnosed before TB), no ART during TB treatment and major side-effects are not baseline differences but on-therapy differences. The baseline variables need to be adjusted for multiple comparisons (bonferroni or benjamini-hochberg).

Response:

Thank you for the observation, we have reworked the sentence to include at baseline and during follow up….

Furthermore, we have conducted the cox-proportional hazard for baseline variables with ART use during TB treatment, major side-effects, and opportunistic infections included as time updated variables.

"there were no deaths after six months" Were patients followed after six months? The methods don't mention that.

Response:

Thank you for the observation, the primary outcome was mortality, defined as any death that occurred during TB treatment, which varied from 6 months in new TB cases, 8 months in repeat TB cases, 12 months in TB meningitis cases, and up to 18 months in bone TB cases.

In addition, during the treatment of TB, there can be treatment interruption due to major side effects (eg: hepatoxicity…) or patients related reasons (eg: defaulter), in such case the guideline advice to prolong the duration of TB treatment to compensate for missing doses. In addition, there was also a poor compliance to the treatment duration which was observed in some cases as well.

We have reworked the methods and discussion to include these details to make it clear to the readers.

"patients with no ART use during TB treatment were more likely to die with(sic) the first two months" This comparison of time to death based on ART implies that lack of ART may have caused early mortality. But if their CD4 was >50, were they supposed to receive ART before two months? It could be the other way around, that patients died before they could be initiated on
ART rather than a lack of ART causing an early death and this is just lead-time bias. Again, your analysis should be stratified by CD4.

Response:

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.

Of the 300 patients included in the study only 83 patients were ART naïve at the time of their TB diagnosis. CD4 count was not stratified among ART naïve patients to analyze the relation with timing of ART initiation and mortality as so much data were missing. Hence, we limited our analysis to assess the benefit of integration of ART into TB treatment.

Furthermore, thank you for the observation we acknowledged that this could lead to lead-time bias and we will include it as a limitation of this study. Although, 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.

Discussion

Line 173:

"There are substantial gaps in the delivery of HIV-associated care in Botswana, despite national policies," Please be specific about what gaps you mean. Are patients started on ART too late? You haven't described the national policies, let alone how they were not implemented.

Response:

Thank you for the observation, we have described the national policies under methods and we reworked the paragraph as follows:

“Our study showed that the burden of HIV-associated TB and related mortality is still high. There is a substantial increase of implementation of Cotrimoxazole preventive therapy with an uptake of 100 %, however there are still gaps in the implementation of ART policy for HIV-associated TB patients despite the national policies, strategies and guidelines”

Line 181:

You are advocating for giving IPT to these patients but as you discuss in the next paragraph, 40% were diagnosed with TB within 3 months of starting ART, so they probably had active TB
at the time of starting ART. If you had given those 86 patients INH along with their ART they would have been on monotherapy for active TB. I think your data better supports your conclusion in the next paragraph for better diagnostics rather than for IPT and the order of these two paragraphs should be reversed.

Response:

Thank you for the observation, we have reversed the order of the two paragraphs.

Line 191:

It is not "intensified active case finding" if done at clinic visits. That's passive case finding. And be more specific about strategies. Urine LAM screening (how many in your cohort had a CD4 of < 100?)? Symptom screening (different sensitivity in those on or off of ART)? Sputum Xpert or smear screening?

Response:

Thank you for the observation, we have corrected, we intensified case finding both active and passive since it is HIV high burden setting. In the cohort, 80 patients had a CD4 count < 100.

We have reworked an entire paragraph to describe further the strategies as follows:

“

The 4-symptom (current cough, night sweats, weight loss, fever) screening tool incorporated the WHO guidelines for intensified case finding has poor specificity and sub-optimal sensitivity, a meta – analysis of around 10,000 HIV positive patients found that reporting at least one of four symptom had an overall sensitivity of 79 % and a specificity of 50 % during active screening for TB. Therefore, due to poor specificity a large numbers of identified patients may require further diagnostic evaluation. Moreover, the sub-optimal sensitivity means that 10 % - 20 % of asymptomatic patients with active TB are missed. Furthermore, The Xpert MTB/RIF assay greatly increased case finding compared to smear microscopy, diagnoses all smear-positive cases and approximately 40% - 70 % smear-negative culture-positive cases with a very high specificity, rapid TB diagnosis and detection of rifampicin resistance. In addition, the urine based assay may be used to assist in the diagnosis of TB in HIV positive adult in-patients with signs and symptoms of TB who have a CD4 count ≤ 100 cells/µL, or HIV positive patients who are seriously ill regardless of CD4 count or with unknown CD4 count. (Seriously ill is defined based on 4 danger signs: respiratory rate > 30/min, temperature > 39°C, heart rate > 120/min and unable to walk unaided). Moreover, the screening of all HIV positive in-patients using urine-
based assay could substantially reduce the risk of being discharged from hospital with undiagnosed TB.

Line 203:

Again, timing of ART initiation is a crucial factor, so simply making it a binary variable of started vs not started is too simplistic. You might look at started per guidelines versus not, but again there is a bias where people are dying before guidelines would say to start ART and you haven't adjusted for baseline severity of disease.

Response:

Thank you for the observation, we have conducted as suggested a Cox proportional hazard regression to adjust for baseline severity. But CD4 count was not stratified among ART naïve patients to analyze the relation with timing of ART initiation and mortality as so much data were missing. Hence, we limited our analysis to assess the benefit of integration of ART into TB treatment.

However, 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. In addition, according to the Botswana guideline during the study period, each HIV-associated TB patient was supposed to be commenced on ART by the end of initial phase of TB treatment.

Line 205:

"poor implementation of clinical guidelines" You appear to have the data to answer this hypothesis. Was ART started according to guidelines?

Response:

According to the Botswana guideline during the study period, each HIV-associated TB patient was supposed to be commenced on ART by the end of initial phase. Of the 83 HIV-associated TB patients who were ART naïve at the time of TB diagnosis, only 43 patients were commenced on ART during TB treatment.

Line 206:

"Inadequate clinical monitoring" I'm not sure what this refers to. Were clinicians reluctant to start ART because they didn't have access to clinical monitoring?
Response:

This refer to the clinical monitoring of HIV-associated TB patients by clinicians, which includes timely ordering of laboratory, monthly review for treatment adjustment and an optimized case management.

Line 206:

"These findings highlight the gap in the delivery of HIV-associated care in Botswana despite national policies, strategies and guidelines and the overwhelming evidence base of the benefit conferred by early initiation of ART and integration of ART and ATT treatment" Without presenting data on how clinical guidelines were missed (eg time to ART initiation) you can't support this conclusion.

Response:

Thank you for the observation, as we have previously said that during the study period Botswana had adopted WHO 2011 guideline which recommended the integration of ART into TB treatment and the early initiation of ART during TB treatment.

Furthermore, we have shown that of the 300 patients included in the study only 83 were ART naïve at the time of their TB diagnosis, the remaining (217) patients had been on ART prior TB diagnosis. Of the 83 HIV-associated TB patients who were ART naïve at the time of TB diagnosis, only 43 (48 %) patients were commenced on ART during TB treatment, which means more than half of patients in need of ART were not initiated on ART during the study period.

Line 218:

"could include baseline and serial screening of other opportunistic infections using improved diagnostic tools such as blood cultures, cryptococcal antigen screening and full blood count, as well as the early initiation of ART, treatment options for co-infection and close clinical monitoring of side effects." Besides early ART, is there evidence for any of these interventions having a mortality benefit?

Response:

The contribution of other opportunistic infections such as cryptococcal disease and cytomegalovirus, bacterial infections, unexplained anemia, and hepatotoxicity to mortality in patients with HIV-associated TB had been well documented to be substantial. Therefore, optimizing the HIV-associated TB case management by the screening and treatment of co-
morbidities and monitoring of side effects could substantially improve survival in HIV-associated TB patients.

Line 222:

"The findings of this study suggest that in Botswana there is a still a gap between knowledge and translation of TB/HIV research findings into routine practice by policy makers and little implementation of national policies, strategies and guidelines on the ground by clinical care providers" This is not supported by your analysis, and also holds clinicians in 2013 to 2019 standards.

Response:

Thank you very much for the observation, we have removed this from the text. Furthermore, we have tried to more focus in the gaps that we found during our analysis. In addition, despite all the evidence regarding the benefit of IPT, the management of latent TB among high risk population in Botswana is still up to date limited to children.

Although, the data presented in this study were for 2013, we have done our best to see if there was any change with the current trend of all key issues presented in this study in the district (2018) report, the WHO TB global (2018) report for Botswana. Therefore, we strongly believe this manuscript will provide a programmatic insight of HIV-associated care in Botswana, to health care providers and policy makers; this will probably contribute to their efforts in helping the country to achieve the 90-90-90 targets.

Table 1:

This needs to be adjusted for multiple comparisons or have a multivariate analysis (logistic regression). It is also missing subscript e. The variables "No ART use during TB treatment", "OI other than TB" and "Major side effect" are not baseline variables.

Response:

Thank you for the observation, we have conducted the cox-proportional hazard for baseline variables with ART use during TB treatment, major side-effects, and opportunistic infections included as time up-dated variables. In addition, we have reworked the table title to include baseline and follow up. The subscript e was added as well.
Comment:

Again, this splitting of the groups is too simplistic and introduces bias that those alive long enough to receive ART are included in the ART group. Additionally, does it make sense to continue the curve out to 20 months if the vast majority were followed for < 10 months? According to the methods it seems they should have only been followed for 6 months.

Response:

Thank you for the observation, the primary objective of this study was to assess the implementation of ART and CPT Policy in a real world setting in Botswana and its relationship with death. While the CPT uptake among HIV-associated TB patients was at 100 %, the ART uptake was at 84 %. Therefore, we had decided to analyze the survival curve among those on ART and those not on ART, since the integration of ART into TB treatment has been found in many studies to improve survival among HIV-associated TB patients. Furthermore, even after adjustment in multivariate, the use of ART during TB treatment was significantly associated with improved survival. However, we could not analyze the relation with to timing of ART initiation and CD4 stratification as much data were missing.

Comment:

The results section states that there were no deaths after month 6, but the survival curve has a significant step after month 10.

Response:

Thank you for the observation, we have corrected the text in the results section.

Comment:

Additionally, does it make sense to continue the curve out to 20 months if the vast majority were followed for < 10 months? According to the methods it seems they should have only been followed for 6 months.

Response:

We have included in the survival curve each patient included in this study as we have described in the methods under statistical section. Furthermore, the primary outcome was mortality, defined as any death that occurred during TB treatment, which varied from 6 months in new TB cases, 8 months in repeat TB cases, 12 months in TB meningitis cases, and up to 18 months in
bone TB cases. In addition, during the treatment of TB, there can be treatment interruption due to major side effects (eg: hepatotoxicity…) or patients related reasons (eg: defaulter), in such case the guideline advice to prolong the duration of TB treatment to compensate for missing doses. In addition, there was also a poor compliance to the treatment duration which was observed in some cases as well.