Reviewer's report

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

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Reviewer: Patrick Cudahy

Reviewer's report:

"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.

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

Abstract:

Line 38: "the implementation of specific interventions", What interventions? No interventions are mentioned in the methods. Please 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?
What about changes in diagnostics for TB that are more sensitive in HIV/TB coinfection? Was geneXpert in use during this time?

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.

Methods:

Line 96: Which interventions?

Line 103: What was the ART policy for those without TB?

Line 104: Would simplify to say that "IPT was not recommended for adults."

Line 109: "the mother's clinic" Is this the pre-natal clinic? I'm not familiar with the term

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.

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.

Line 114: "Laboratory" Please be more specific. I assume smear, culture, and/or Xpert.

Line 114: Were these all pulmonary TB or were there extrapulmonary? Did they all get drug-susceptibility testing? Did any have MDR or XDR?

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

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.

Results:

Line 146: What was the median follow-up time?

Line 152: What ART regimen were they on?
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).

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

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).

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

"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.

Discussion

"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.

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.

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?

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.

Line 205: "poor implementation of clinical guidelines" You appear to have the data to answer this hypothesis. Was ART started according to guidelines?

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?

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.

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?

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.

Conclusion

Line 244: "the epidemic of HIV-associated TB still continues to rage despite policies, strategies and guidelines" This is too broad and non-specific. Your study shows that mortality in HIV and TB co-infection remained high in 2013.

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.

Figure 2: 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. The results section states that there were no deaths after month 6, but the survival curve has a significant step after month 10. 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.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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