Reviewer’s report

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

Version: 1 Date: 18 Apr 2019

Reviewer: Rachel Kubiak

Reviewer's report:

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.

ABSTRACT

Line 53: State the difference in survival time.

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.

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.

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.

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

Line 80: Should read "...HIV/AIDS patients in sub-Saharan Africa indicates that HIV-associated TB..."
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%.

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

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.

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.

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

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

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?

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.

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

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.

RESULTS

Throughout, choose 0 or 1 decimal points and be consistent (e.g. lines 185-187 have results with 0, 1, and 2 decimals).
Line 184: Related to line 140, why were 88 TB-HIV patients not included?

Line 194-5: 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.

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

Line 201: add p-value for opportunistic infection.

Line 205: Table 2 has p-value for OI at <0.001.

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

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.

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

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.

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

Line 241: A urine-based LAM assay, not any urine-based assay. Good to cite the WHO policy guidance for LAM.

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.

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

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

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

Another limitation is lack of testing for drug resistance especially among retreatment cases.
TABLES 1, 2
- Order variables in the same way.
- List like variables together (e.g. No ART use during TB treatment and ART naïve).

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.

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

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

Yes

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

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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