Author's response to reviews

Title: Integrating intensified case finding of tuberculosis into HIV care: an evaluation from rural Swaziland.

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Author's response to reviews:

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Dear BioMed Central Editorial Team,

Thank you for your consideration and peer review of MS: 1197503832442850. Integrating intensified case finding of tuberculosis into HIV care: an evaluation from rural Swaziland.

We have addressed the editorial comments and peer reviewer questions to the best of our ability in the points below. We have revised the manuscript accordingly using “tracked changes” and our styles are correctly formatted.

Editorial comments and responses

1. Please provide an email address for each author on the title page.
   • Yes. This is now provided.

2. Please provide a statement in your Methods (ethics) section regarding informed consent.
   • Yes. Statement included on bottom of page 9.

3. Please submit the original versions of your figures as separate files, as the versions embedded in the manuscript document have become pixellated.
   • Submitted separately as Jpeg files.

REFEREE 1 Comments and responses

1. Methods, page 5: Could you please describe the services available at the
hospital and clinics a bit more in detail? Do the clinics provide ART – if yes on the bases of clinical staging or on the bases of CD4 counts?

• ART treatment was initiated at the hospital and clinics provided ART “Roll out”. The details are added on the bottom of page 5.

2. If the clinics provide ART on the bases of CD4 counts – where are the CD4 counts analyzed?

• The weekly transportation system to the hospital is included in the description also.

3. It seems that TB diagnosis (even in HIV-infected individuals) at clinic level was only implemented at the time of the study. Did the clinics refer patients for TB investigations to the hospital prior to the study? Is there a X-ray machine available at the hospital?

• This is now clarified on page 6.

• In questions 1-3 above, the referee makes an important point that we need to better explain the difference in TB and HIV service provision at both the hospital and the clinics. The additional text on page 6 should provide a better description.

4. Please describe the differences between the hospital and the clinics – are both settings operating a provider-initiated HIV testing service? Did you include all patients (inpatients and outpatients) diagnosed with HIV in the hospital – one would expect patients accessing the hospital to be sicker than patients accessing the clinics.

• Page 6 now emphasises that both hospital and clinic settings provided provider-initiated HIV test.

• Page 9 states more explicitly that hospital inpatients were excluded from the study. Our earlier analysis suggested a complex relationship between the demographics of attendance and choice of screening site (hospital or clinic). For example, analysis using CD4 counts and clinical staging did not suggest that patients who attended hospital screening were not necessarily sicker. Some simply lived closer to the hospital or it was accessed significantly more by men who were working in the town of the district hospital. We excluded this analysis due to its overall lack of contribution to the overall findings and conclusion.

5. Methods, page 8: “We analysed the probability of initiating TB treatment within one month of diagnosis using logistic regression. Predictors of time to diagnosis and treatment were analysed using Kaplan-Meier survival curves, log-rank tests and proportional hazards models.”

In the result section the author state that the proportion of starting treatment within one month of a smear positive diagnosis was not significantly different between the hospital and clinic groups. They also speak about the median time from diagnosis to treatment. Thus it sounds like a simple #2 test or t test for difference in proportions and maybe a Wilcoxon test for difference in medians was used to do the analysis.
Yes, we have now performed Chi square test for differences in proportion.

For the difference in median. A log rank test was performed and proportional hazards analysis was used to adjust for confounder. After reviewing this analysis, we decided to exclude this from the revision because the time difference of 6 days is statistically significant but not of strong relevance to the overall conclusions of our paper on screening.

6. In addition in the title of table 1 the authors state that the comparison was performed by “univariate logistic regression”. Again I think a #2 test for differences in proportions and a Wilcoxon test for differences in medians (e.g. for age and distance from the hospital) would be more appropriate.

We have now performed Chi square test for differences in proportion and log rank for the differences in medians. The logistic regression in Table 1 was used to compare baseline characteristics of the two groups.

7. Results, page 9: “Sputum-smear positive case detection rate was 2% overall giving a number needed to screen (NNS) of 52.” The authors used the total number eligible for screening as the denominator to calculate the case detection rate. I completely agree with this approach, please state your denominator clearly in the results. However a lot of studies use the number participating (or submitting sputum) as their denominator. Thus when comparing the yield of TB found in this study with other ICF studies in ART or VCT sites the difference in denominator should be part of the discussion.

We have stated the denominator more explicitly in the result section on page 10 (Results: Performance through the pathway).

In the first paragraph of the discussion (pg 11-12) we have now explained the rational for the use of our denominator and the implications of this.

8. In addition most of the ICF studies in ART or VCT clients were performed as part of a research project and therefore had more resources and a lower attrition rate. This study shows that motivating individuals to submit sputum samples is difficult. I think this should be stressed in the discussion. However despite this difficulty the authors were able to diagnosed 28 cases among individuals who submitted sputum samples. Thus the yield among individual submitting sputum samples was 28/172 (16.3%). Please comment on that very high yield in TB suspects. The expected yield in TB suspects is around 10% (resources are allocated on the bases that 10% of TB suspects are expected to be smear positive).

Yes, we have now included and emphasised this point in the results, and in the discussion.

9. Results, page 9: “There was no significant difference between the hospital and clinics sites in smear positive case detection rates (OR = 0.48 (0.21-1.15); p=0.10)). The number needed to screen (NNS) in order to detect one new case of AFB smear positive TB was 34 cases in clinics as compared with 64 cases in the hospital. The NNS for one treatment initiation was 38 in clinics and 75 in...
hospital.”

This paragraph is a bit difficult to understand. It would be easier to first state that the proportion of individuals identified as TB suspects in the hospital (18%) was significantly different to the clinics (49%) (I would use a #2 to compare those two proportions) Why? This should be part of the discussion.

• Yes, we have stated the proportion of suspects as the first sentence and followed the pathway in a more logical format presenting NNS at the end. We have used Chi squared test for the calculations.

• A paragraph has been added to the discussion on some of the potential explanations for the higher proportion identified as suspects.

10. The proportion lost to follow-up between identifying them as TB suspects and submitting the sputum was similar in the hospital (45%) and clinics (50%). However the yield of TB in patients submitting sputum samples was 20% in hospital TB suspects and 12% in clinic TB suspects. – Why? – This should be part of the discussion.

• We have included this in the results, however, this difference was not statistically significant ($x^2 = 1.55; p =0.21$). Therefore the difference was not highlighted for further discussion.

11. Results, page 10: “Demographics and characteristics”
Please consider calling it “demographics and characteristics of individuals diagnosed with TB”

• Yes. This has been corrected.

12. Results overall:
One of the main findings is that there is a considerable drop out between being identified as a TB suspect and sputum samples submission. I think it would be really interesting if the authors investigate risk factor of not submitting sputum samples (e.g. age, sex, immunestatus). The knowledge of potential risk factors could inform the program to pay special attention to certain patients groups.

• Our earlier draft contained more extensive analysis of demographics and risk factors. We also conducted focus interviews with a small sample of those who did not submit specimens. We also examined physical distance and geographical distance from clinics and the hospital. We agree that comparing those who did not submit specimens with those who did would provide interesting findings. Unfortunately we were unable to do this analysis in this paper

13. If the data is available it would be interesting to know how many of the eligible individuals were newly diagnosed with HIV and how many were in routine pre-ART care. Was being newly diagnosed with HIV a risk factor for not submitting sputum samples?

• We agree that this would be interesting and would add to our understanding of
those people screened, TB suspects and those not submitting. We were unable to distinguish between these two groups through our existing data. This is explained on page 14. With this study, we felt that the strength was in showing the results and feasibility of the overall pathway and implementation of a real-life programme. Therefore we limited our data collection to keep the intervention operationally focused.

Discussion, page 11: “One potential solution would be increased use of spot sputums and at the hospital, real time microscopy”. Please consider sputum induction as a possible mean to get sputum from individuals otherwise unable to produce a sputum. Real time microscopy would not reduce the loss between identifying individuals as TB suspects and sputum submission it would just decrease the time between submission and diagnosis (and possibly treatment initiation).

• Yes, this has now been corrected on page 13.

Discussion, page 11: “In this ICF programme, TB treatment was available only at major centres including the district hospital”. Please remove the “g”.

• Yes, now corrected.

Figure1: “Patients is given result on the day they return and advised to see a physician for review and consideration of possible smear negative or extrapulmonary TB”. Please clarify what that means. I am not sure how many physicians are available in rural Swaziland. Would the patient not be sent to the hospital to rule out TB with e.g. CXR?

• This means that patients which had TB symptoms but were smear negative required further evaluation. It is correct that there are very few physicians. However, diagnosing extra pulmonary TB and commencing TB treatment in the absence of a sputum smear could only be prescribed by a physician.

REFEREE 2 Comments and responses

Major Compulsory Revisions

1. The authors misunderstand the definition of "case detection rate”. CDR is defined as proportion of detected case among incident cases. Proportion of TB patients among screened is not the case detection rate.

• We agree on the reviewer’s definition of case detection rate and have removed any reference to CDR. We now refer to our study findings as proportion of those screened who were smear positive.

2. It is not clear if this paper is discussing prevalence or incidence of TB among observed HIV positive (PHW). It is necessary to classify screening/detected cases to i) newly recruited PWH and ii) PWH already in the service. Many studies showed higher yield by the 1st screening or screening at the recruitment (high TB prevalence when they are detected as HIV positive). Rather low TB detection (2% among those screened) in this study might be due to higher proportion of
follow up cases (known PWH) and very short observation period.

- We were screening HIV patients to detect new cases of smear TB and test the feasibility of ICF. We agree that there is an important distinction in the results between the newly recruited PHW and those already in HIV care. In this study, we were unable to separately classify these two groups of PWH using our routinely gathered data. We agree that it is important to highlight this and have added this to the section on limitations (pg 14).

Minor Essential Revision

3. High drop out in the screening and diagnostic process is a great concern. The authors have not shown if they dropped out from the HIV follow up service itself or simply from the TB screening and diagnostic process. Please clarify.

- We agree that this is an important distinction. Our results of the drop out rate on screening and diagnosis relate to the ICF programme only. This clarification has been added to the discussion on page 12.

4. Purpose of the analysis in table 1 is not clear without comparison between TB patients and non-TB patients.

- Comparing TB patients with non-TB patients would be an interesting comparison to consider. Our sample size of those diagnosed with smear positive TB is small (n = 28) and the time period was also short. Because of this, we felt it was better to provide the broad comparison of those attending ICF services and to distinguish those attending clinics versus the hospital. In this feasibility study we aimed to understand the demographics of those populations attending screening in order to provide better performance management of the programme. This was to inform future design of ICF services. We describe the stages and overall reality of TB case finding and its integration into routine TB/HIV care in a rural, low income setting where TB screening is often overlooked.

Discretionary revision

5. Age sex adjusted expected number of TB case detection among this 1467 HIV patients could be calculated from routine surveillance data. It may tell if this intensified screening programme could detect TB cases more than routine programme or not, although small sample size and very short observation period is concerned.

- This would provide interesting analysis and help explain the type of service required and whether ICF is better at detection than routine care. We were unable to perform this analysis of age sex adjusted expected number from routine data. The focus of the paper was to explore the feasibility of implementing a programme with limited resources in a rural, low income setting. A critical aspect of this was to explore provision of ICF in community clinics which previously provided no TB screening services. Additional content has been added to the methods (setting) section to provide a better understanding of the existing TB services.
We hope that these revisions in the paper and our explanation in this letter have provided further clarity to reviewers. If any further changes or clarifications are needed, we are happy to do so.

We thank you again and look forward to receiving your feedback.

Sincerely Yours,

Susan Elden