Author's response to reviews

Title: TB treatment outcomes among TB-HIV co-infections in Karnataka, India: how do these compare with non-HIV tuberculosis outcomes in the province?

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Author's response to reviews: see over
Dear Editor,

Please find below our responses to the reviewers comments. All changes in response to the reviewers comments are highlighted in yellow in the revised manuscript.

Kind regards,

Dr. A De Costa (on behalf of all authors)

Reviewer 1
1. The outcomes reported are only among co-infected patients reporting to ART centers. What is not known are the numbers of TB patients diagnosed to be HIV+ but never making it to the ART centers. The authors should provide this number and if not available, mention it as a limitation. Obviously, the overall outcome will depend on how good the linkage between TB and ART programs is.

Response: Yes, we agree with the reviewer. We had mentioned this as a limitation on page 9 (It is highlighted in the revised version).

2. It is not clear from the manuscript how many of the patients were already on ART at the time of diagnosis of TB. The authors state that 78% of patients were initiated on first line ART - but was this after the diagnosis of TB? They state later that outcomes were better among patients already on ART but they do not provide the numbers or the analysis to support this statement. If possible, 3 groups can be compared - no ART, ART after initiation of TB treatment and ART prior to diagnosis of TB. Analysis would have to control for CD4 counts in the 3 groups.

Response: All coinfected patients in the study were registered at ART centers (the data set is secondary data from the ART centers). Therefore these patients at the time of TB diagnosis were either (a) pre-ART (i.e no ART) or (b) already on ART (ART prior to diagnosis). The 78% figure we have quoted refers to group (b). We have clarified this now in the results section on Pg 6. We thus had only two groups. Median CD4 counts were 161 and 140 cells/mm³ in each group respectively.

3. The authors have provided proportions and crude odds ratios comparing outcomes among TB patients with and without HIV co-infection. A multivariable regression model would provide more reliable results after controlling for all confounding factors.

Response: Yes, we agree it would have been better to do a multivariate regression comparing outcomes among TB-HIV infections and TB infections alone. However the data from the TB program from which this analysis was derived did not have any information on predictors other than outcomes, which restricted the possibility for a multivariate analysis. We have clarified this by stating in the methods section on page 5 that only summary statistical reports were available from the TB program

4. If authors want to show the impact of ART on TB treatment outcomes, they should analyze results by time of initiation of ART after ATT.

Response: Yes, we agree with the reviewer on this. We also wished to do this, however the data set from the ART program has too many missing dates to be able to reliably to tell the time between initiation of ATT and ART. The variable we did have was a categorical one which told us whether a patient was pre ART (not yet started on ART) or already on ART at the time of diagnosis. Hence we were confined to using only this variable. We have included this now as a limitation on pg 9.
5. Figure 1 is not required
Response: Yes, Fig 1 can be removed.

6. Title can be shortened and simplified
Response: The title has been shortened and simplified. It now reads ‘TB treatment outcomes among TB-HIV co-infection in Karnataka, India: how do these compare with non-HIV tuberculosis outcomes in the province?’

7. Conclusions in Abstract suggest that early initiation of ART improves outcomes - however the time to ART initiation has not been analyzed in this paper. This should be modified.
Response: This has been modified to read ‘Co-infected patients already on ART demonstrated better TB outcomes in than those not on ART.’

Reviewer 3

1. How you counted patients (TB patients, co-infected patients on ART, co-infected patients not on ART).
Response: Yes, every ART center has in its registers the HIV infected patients registered at the respective center who are on TB treatment. This information is filled in by staff at the respective ART centers. These staff provide reports on co-infected patients to the provincial level ART program office, from where these spreadsheets of data on co-infected patients were obtained.
Similarly TB program data from the DOTS program across the province flows in from the peripheral DOTS centers to the provincial program office. The reports (unlike the coinfected patient reports) are only summary statistics of patients by outcome, and so not contain individual characteristics of each patient. We have elaborated this in the methods section on pg 5.

2. How you made sure that none of the three groups were double counted.
Response: This is a very important point raised by the reviewers. While we can be certain there is no overlap between the patients not on ART and those on ART at the time of the TB diagnosis (ART sites take care of HIV infected patients who are and who are not on ART), it is likely that co-infected patients are included in the main DOTS program registers, though in those reports they are not identifiable (co infection identification is from the ART program) as these are summary statistical reports from the TB program. So yes, there is the likelihood of overlap there as co-infected patients are not removed from the registers, and hence a bias. We have now mentioned this in the limitation section on pg 9.

3. If there were some uncounted patients, how this may have biased the results.
Response: We have stated in the limitations that there could be uncounted patients, particularly those receiving care outside the programs in the heterogeneous private health care sector. Treatment outcomes can vary widely in this sector. While we have acknowledged this as a limitation and are aware that it would create a bias, it would be difficult to state how this could bias the results, as it is quite impossible to know what treatment outcomes for patients treated outside the program would be.

Minor Essential Revisions

4. Table 1: "before and after initiation of ART" does not seem to be accurate. The text says that everyone with CD4 < 350 were eligible for ART, so this title ought to read something like, "Patients taking and not taking ART".
Response: Yes, this has been changed.

5. "Rates of death and failure were significantly higher among TB only patients than in the TB HIV co-infected cohort" Table 2 shows that Default and Failure are higher, not Death and Failure.

Response: Reads default and failure

6. The issue of retreatment is an interesting one. Are there any DRS results that would shed light on the issue of relative rates of drug resistance in non-HIV and HIV co-infected patients?

Response: Unfortunately no, DRS tests are not done routinely under the program.

Discretionary Revisions
Please explain what is a "link-ART centre"
Response: ART Link centers - these are centers further in the hinterland which serve as points where patients living in these areas can collect their medication to reduce travel time and opportunity costs for patients). This has been explained now on page 4.

Reviewer 3

I don’t think that outcomes from this study can allow to concluding as in the abstract “The benefit of early initiation of ART among co-infected patients is demonstrated by the improved TB outcomes in this population.” No study regarding early or late ART initiation was conducted in the methodology. Otherwise the authors have to show this particular data in the result section. In addition, this content in the discussion section should be revised.

Response: Yes we agree. This is the same comment as comment no. 7 (reviewer 1) and comment no. 4 by reviewer 2. We have modified the discussion to reflect this as well.

2. Data on TB culture and drug resistance is still lacking in this study. This factor has a great impact on TB treatment outcomes. I understand that not all patients had this test done. The authors may show only the patients who had drug sensitivity result.

Response: this is the same as comment 6 raised by reviewer 2. Unfortunatley we do not have drug susceptibility tests for any patients.

3. What proportion of patients 1. who had received ART and subsequently developed TB and 2. those who diagnosed TB first and started ART later. This data needs to be shown in the result section because survival outcomes of both groups are different.

Response: Patients at the time of TB diagnosis were either (a) pre-ART (i.e no ART) or (b) already on ART (ART prior to diagnosis). We have stated that 78% figure we have quoted refers to group (b).

4. Is there any DOT program implemented during the study period? If so, give the details. In addition, adherence data should be shown.

Response: Yes there was a DOT Program in the province at the same time. This is stated at the top of page 5. Adherence data is not reported in the TB Program reports.
5. The timing of CD4 cell count measurement should be mentioned in the result, how many weeks or months before or after TB diagnosis.

Response: we have not commented on this as the CD4 counts are done periodically and the program reports contain the last CD4 count, this is therefore not at the same point in time for all patients relative to the dates of TB diagnosis.

6. In the discussion section, the authors mentioned that “While overall treatment success rates in our co-infected cohort were close to 75%, they were significantly better in the group that had been already initiated on ART compared to those who were not on ART.” It would be better if the author discuss more regarding the reason to explain and give the suggestion to improve the outcome.

Response: In the text, in reference 15-18, we cite the randomized trials published in the New Engl J Med that supported this strategy which was subsequently recommended by the WHO and now adopted by the Indian program.

7. It would be more beneficial if all risk factors for death in multivariate analysis can be shown, instead of univariate analysis only.

Response: This is the same as comment no 3 by reviewer 1. we agree it would have been better to do a multivariate regression comparing different outcomes including death. However the data from the TB program from which this analysis was derived did not have any information on predictors other than outcomes, which restricted the possibility for a multivariate analysis. We have clarified this by stating in the methods section on page 5 that only summary statistical reports were available from the TB program.

Minor comments
8. What is the reason that the study period was different between TB/HIV group (April 2010-March 2011) and TB mono-infection (April 2010-December 2010)?

Response: this is because at the time of analysis, data on the last quarter of the year (dec2010-Mar 2011) was not available at that time. However previous reports indicate that data does not vary significantly between quarters of the year.

9. Table 1 and table 2: a sum up of number of patients “not on ART” and “on ART” is 5040 (1024+4016) patients but it was not corresponded to table 2 (5079 patients). Please clarify.

Response: This discrepancy is because in table 1 – there were missing values for ‘ART/not on ART’ variable for 39 patients. Therefore these patients are not shown in the table 1. However we know that they are co-infected patients so they show up in table 2.

10. The authors showed in the 2nd paragraph of result section that there were 5079 patients after excluding ongoing treatment that I agree but why a total number of treatment outcome was not corresponded (3776+296+22+797=4891).

Response: this is again because of missing values for the treatment outcomes for 188 of the 5079 patients. Therefore these patients have been excluded in the analysis, though we are sure that they were HIV-TB co infected.