Author's response to reviews

Title: Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in addis ababa: a case control study

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Author's response to reviews: see over
Authors Response for Reviewers.

Reviewer I: Rawleigh Howe

Dear Rawleigh Howe,

We would like to thank for the valuable comments you gave us. We are very grateful and your comment made our paper stronger. We have addressed all the comments and a native professional editor has edited the manuscript.

1. More information on the patients in the MDR cohort would be helpful. Do they have confirmed MDR TB? Most had multiple episodes of TB previously, but what had been the treatment outcomes of those prior illnesses? How about those with a single TB illness—are we to presume this illness as the one they were currently undergoing therapy for? This is relevant to the study questionnaire and design, because it is not clear whether the answers given in the structured question refer to their most recent illness, all of their illnesses, any of their illnesses, or – as sometimes implied—their “first” course of TB therapy. How might this influence the results obtained?

Response: We elaborated the cases and controls further in the manuscript.

The MDR-TB patients (cases) were diagnosed through culture and DST in the Ethiopian Health and Nutrition Institute and were on treatment for MDR-TB during the study period. The controls were previous TB patients who completed their treatment and declared cured or treatment completed two years back from the study period. So in the control group they were not under treatment during the study period. It is true that most study participants in the case group had multiple episode of TB previously but as most study participants in the control group had one TB episode we only used for the analysis their first time TB treatment outcome. It is elaborated in the manuscript. Questions on Tuberculosis treatment related condition assess the study participants first course of first line TB treatment. In the recruitment of the study participants section “their first course of first line TB treatment” is added to describe it. Since some of the study participants have more than one TB episode, there might be recall bias. This was mentioned in the limitation of the study part.
2. That MDR patients have a higher fraction of prior category II therapies is virtually guaranteed (not merely a "possibility") from the study design, since, by definition many would or should have gone onto such regiments given national policy for previously unsuccessful therapy, whereas few among the control cohort would have since they were preselected among those with positive outcomes.

Thus, although there are good reasons to believe this could have contributed to MDR emergence, the association in this study could be purely fortuitous. The assertion that more attention to drug testing among high risk individuals should be applied in Ethiopia rather than immediately starting on category II is obviously important, but it might be helpful to cite the positive benefits of category II when given in the correct context. Overall the discussion of category II could be better developed and written.

**Response:** The national guideline is to have culture and DST for all first-line treatment failures or who do not convert after three months. But that is not happening in Ethiopia because of there are no culture and DST facilities to address for all patients. Therefore health facilities start category II treatment regimen without knowing the drug sensitivity status of the patient. With the expansion of culture facilities and GeneXpert, the current recommendation will be more applicable and we included in the manuscript.

3. The composition of the control group from health centers from which MDR patients had been referred is a reasonable approach. The authors state that such subjects were selected “randomly”. How was random selection done? More detail should be given.

**Response:** The sampling method is elaborated in the manuscript in the following manner: “Prior to identification of the controls, five health facilities were identified based on the number of MDR-TB cases that they referred to St. Peter Hospital. The same number of controls was selected from each of these five health facilities. The sampling frame comprised all patients who had completed first-line anti-TB treatment and were registered as cured or treatment completed. Following this sampling frame, the required sample size of the control group was selected using systematic random sampling. When a selected patient declined to participate in the study, the next person in the register was taken.”

**Reviewer's report#2**

Dear Anil Pooran,
We would like to thank for the valuable comments you gave us. We are very grateful and your comment made our paper stronger. We have addressed all the comments and a native professional editor has edited the manuscript.

**Major Compulsory Revisions**

1. In the 4th paragraph of ‘Background’, the authors mention the limited availability of tests to detect MDR-TB then give stats on lab capacity for performing smear and culture but do not mention DST. MDR-TB cannot be detected by smear and/or culture alone and there must be some method of drug sensitivity testing that need to be performed i.e. what method was used to detect drug resistance (culture DST, Hain, Gene Xpert?), and what was the lab capacity of doing MDR-TB detection. It is important to state these facts.

*Response: We have incorporated the following sentence in the manuscript: “At the time of this study in Ethiopia, the LPA, or culture using Löwenstein-Jensen media and drug-susceptibility testing (DST) were provided only at the Ethiopian Health Nutrition and Research Institute in Addis Ababa”*

2. In the ‘eligibility of study participants paragraph’, the definition of the study participant groups is confusing and needs to be better defined. Were these MDR-TB patients diagnosed by DST and by what method was used? Were they drug sensitive TB patients who took first line drugs for more than a month but did not respond to treatment? How long have these patients been on first line therapy before being diagnosed as MDR-TB? Similarly, is the control group comprised of TB patients who were recruited after successful completion of treatment? Also, it would be helpful if the TB screening tool mentioned was included in an online supplement.

*Response: “MDR-TB patients diagnosed by LPA, or culture using Löwenstein-Jensen media, and DST at the Ethiopian Health Nutrition and Research Institute and who were being treated at St. Peter Hospital during the study period were considered as cases. In Ethiopia a patient is a suspect for MDR-TB if he/she is a symptomatic close contact of a confirmed MDR-TB patient; a symptomatic individual from a known high-risk group such as health workers; a case of treatment failure; a new TB patient who remains smear positive after 2 months of treatment (for new cases) and after 3 months of retreatment with first-line treatment or retreatment (e.g., return after default, relapse) . The controls were patients who had completed first-line anti-TB treatment and were declared cured or treatment completed using the WHO criteria and adopted by FMOH of treatment outcomes between 9 April 2009 and 28 February 2010 (two years back*
from the study period). Additionally, the controls were those with no clinical symptoms of TB based on the TB screening tool” we attached it online as a supplement.

3. Were the results from the multivariate logistic regression analysis included in the results? If yes then please make the reporting of the outcome of this particular analysis a bit clearer

Response: We have revised the sentences to be more clear and our editor also worked on the language part.

4. In the second paragraph of the discussion, the authors suggest that being a male patient was associated with MDR-TB development as they do not adhere to treatment as well as females. Perhaps the authors can do an association of being male and defaulting from treatment to emphasize and provide evidence for this point. At the very least, the authors can report on the number of defaulters/non adherers that were male.

Response: The male non-adherent number and proportion is added in the result and discussions section.

5. In the third paragraph of the discussion, the authors state that a 2 to 7 month duration of first line anti TB treatment was associated with MDR-TB development. A 6 month course of anti TB treatment is generally considered a full course for treating drug sensitive TB, at least using category I regimen. For this particular group, i.e. patients treated for 2-7 months, it would be helpful to report the median length of first line treatment in these individuals

Response: Sorry the data was collected in ranges of months and difficult to calculate the median. That is the weakness we realized now.

6. In paragraph 8 of the discussion, the authors state that smear negative or EPTB is difficult to diagnose and may explain the association of smear positive TB with MDR-TB development. Do the authors mean that due to lack of laboratory infrastructure to diagnose smear negative or EPTB, there may cases of MDR-TB that are not being diagnosed and, as a result, explain the association of MDR-TB with smear positivity? If so then the authors need to explain their reasoning with a bit more clarity
Response: There was only one national lab to do the culture and LPA and that was a limiting factor. Getting samples for extra pulmonary also requires a qualified professionals and most of the DOTS providing health centers are health centers without such capacity. And For pulmonary cases MDR-TB is diagnosed using sputum sample, which is easier than the extra pulmonary samples.

7. The incidence of adverse drug reactions in HIV+ MDR-TB patient on HAART usually tends to be higher than HIV- MDR-TB patients due to the increased number of possible interactions with the addition of ARVs to the MDR treatment regimen. It would be informative if the authors can do additional analyses to determine if HIV positivity had an association with higher incidence of ADRs, or treatment default.

Response: We did not ask adverse reactions of HIV+MDR TB patients. The study was not aimed to ask the current adverse reactions but during the category I treatment. We feel that there was a gap in our design that we did not ask if the HIV/TB patients were also taking both ARVs and first line anti-TB medications at the same time. We have not also substantiated whether the TB or HIV was the first disease in our study.

9. In table 1, state the median weight of the cases and controls. In table 3, what were the most common drug side effects? Also what was the median duration of the first course of anti-TB treatment?

Response: The most common drug side effect of the study participants was “Vomiting” and it is added in Table 3. We did not take the weight of study participants. As we said above the question for the duration of treatment was framed in ranges and we cannot calculate median duration of treatment.

Discretionary Revisions

19. Perhaps the authors would list the drugs in Category I and II in the text or in table 2

Response: Category I and II drugs are listed in the manuscript
20. It would be informative if the authors include the TB screening tool and the Study questionnaire used in an online supplement.

Response: the TB screening tool is referenced.