Author's response to reviews

Title: Successful MDR-TB treatment regimens including Amikacin are associated with high rates of hearing loss

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Author's response to reviews: see over
Major Compulsory Revisions

General

The authors analysed the risk factors associated with development of hearing loss and the effects of amikacin-based regimens on the treatment outcomes of MDR-TB patients. They showed amikacin is effective for MDR-Tb treatment, but is associated with a high incidence of hearing loss.

Major comments

1. Results; page 9 line 1-2. The authors stated that HIV infection, prior ATT and MDR-TB treatment, baseline renal failure and development of renal failure at any point during treatment were risk factors for poor treatment outcome (Table 4). However, in Table 4, renal failure and MDR-TB treatment were significant and others were not significant. Please, clarify this.

We appreciate the reviewer’s comment and Table 4 shows the factors associated with good clinical outcomes among the entire population and after stratification by the presence or absence of hearing loss (according to the different definitions of hearing loss used in the study). We recognise that results showing factors associated with clinical outcomes among the entire population (without stratification) would be of greater importance. These results show that factors associated with hearing loss are the same than those associated with good clinical outcomes, highlighting the complexities of reaching a balance between effectiveness of the treatment and toxicity. We have added a column showing such results. These data shows that HIV infection and prior ATT were associated with poor clinical outcomes. Given the collinearity between prior history of TB and prior ATT, two different models were built. For clarity, only the results of one of these models are presented in the Table. As the reviewer points out, the association between HIV and prior ATT were not significant after further stratification of the population. We have rectified this in the manuscript.

In addition, clarify that the treatment of MDR-TB means that prior history of MDR-TB treatment before the enrolled this study.

This has been clarified in the text and the Table

2. Results; page 9 line 3-4. The value for aOR are different with Table 4.

We appreciate the Reviewer pointing out this discrepancy. This discrepancy was due to the same reasons mentioned above. This inconsistency has been clarified and the entire document has been revised for full consistency.
3. Table 1. If Table 1 shows the demographics of all participants (n=437) within the table, it will be more informative for the readers. Classification of MDR-TB clinic (clinic1, clinic 2…) is not necessary, if they have the same protocol. Footnotes for the abbreviation are needed.

These modifications have been incorporated as suggested. However, we have left the data stratified by clinic to show lack of clustering by geographic/clinic location. Given the ethnic, social and environmental differences across Botswana, we believe that showing lack of clustering is informative. In this version of the manuscript we make this finding explicit and discuss it in the Results and Discussion sections.

4. Table 2. The authors should clarify the description of number in the Table. AOR (95% CI) is not appropriate. The authors should clarify the description as median or mean, IQR or range in the Table. Footnotes for the abbreviation are needed.

As the reviewer mentions, AOR was a typo which has been corrected. However, the numbers in the table are accurate and they indicate means (averages) or medians according to the presence or absence of normal distribution of the data. The table has been made clearer to indicate the appropriate measures.

5. Table 4. If the authors wanted the show the aOR for the good clinical outcome among MDR-TB patients, they need to revise the table 4 easy to read. In addition, there are discrepancy between the statement in the text and table 4. Footnotes for the abbreviation are needed.

As suggested, Table 4 has been modified for clarity and footnotes have been included. As mentioned, all discrepancies have been corrected.

Minor comments
1. Results; page 8, line 11. There are some typographical errors for %. There are discrepancies with Table 1. Those with no documented hearing loss, treatment success was 60 (60%) whilst 29 (29%) were …

As suggested, this is an error and the discrepancies have been fixed.

2. Results: page 8, line 22-23. The value of aOR for the duration and dosage of amikacin are different with Table 3.

As suggested, this is an error and the discrepancies have been fixed.

- Level of interest: An article of importance in its field
- Quality of written English: Acceptable
- Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
- Declaration of competing interests: I declare that I have no competing interests
WHO recently recommended extending the duration of injectable drug use from 6 to 8 months, as longer use of injectables has been found to be associated with more successful treatment outcomes. However, optimal duration of injectables, in terms of balancing the efficacy and adverse effects, is an important but controversial issue in MDR-TB treatment. In general, given the importance of the subject matter and the large number of patients included in the study, the manuscript makes a contribution to the field.

My specific comments are as below.

1. What is the valid denominator in the assessment of treatment outcomes (good vs poor)? Out of 437 MDR-TB patients 28% (n=124) were still on treatment. They were excluded in the primary and secondary analysis. However, according to the revised definition by WHO, majority of cases on treatment will be assigned outcome. In addition, the end of enrolment and observation is just same (June 30, 2012) in the manuscript (p7 line 28). I wonder whether majority of patients on treatment had the sufficient follow-up time for outcome analysis. I am not sure it would proper study design to include the patients still on treatment. Hopefully the authors can provide some explanation.

We appreciate the reviewer’s concern and suggestions. A characteristic of longitudinal analysis is that data are usually censored. Censoring occurs when incomplete information is available about the time to the event of some individuals (e.g. patients who are lost to follow up or those who are not followed until treatment completion). With few exceptions, the censoring mechanisms in most observational studies are unknown and hence it is necessary to make assumptions about censoring when the common statistical methods are used to analyse censored data.

Our analyses included all patients at risk for ototoxicity. Our implicit assumption is that all patients have an equal risk of development of ototoxicity at any point in time. Since patients on treatment are at risk for the development of the outcome, we decided to include them. We acknowledge that this assumption might not be absolutely true (give potential differences in susceptibility and other confounders). However, after adjustment for confounders and particularly time in the study, we believe it provides the most robust analyses to look into the relationship between aminoglycosides and ototoxicity. This point has been clarified and expanded in the discussion of the new version of the manuscript.

In addition, our study has what is called “right censoring” of the outcomes. Right censoring occurs when a data point is above a certain value but it is unknown by how much. In our study we measure the occurrence of outcomes at a predetermined time, regardless of whether the patients have finished
their AG treatment or not (also called Type 1 censoring). Patients who were included in the analyses without finishing treatment are considered to be “right censored” given the fact that we don’t know with certainty their clinical course after the cross-sectional time defined for “termination” of their follow up period. We have clarified the definition of censoring in this version of the manuscript.

2. Did the authors assess the previous use of AG as a risk factor for hearing loss? Previous use of aminoglycoside is a known risk factor for ototoxicity. A total of 268 (61%) patient had treated with aminoglycosides prior to enrolment in this study. As shown in table 1, none of the patients with no documented hearing loss were previously treated with MDR-TB regimen, probably including aminoglycoside. Please clarify this issue and add some comments in the discussion section if necessary.

As suggested, this has been fixed and reflected in all, the tables. Unfortunately our data regarding overall prior use of AGs is incomplete and inconsistent. However, as the reviewer points out, prior history of MDR-TB treatment is a good surrogate for prior AG treatment. We expand the discussion of this point in the Discussion section.

3. The authors should provide their policy and procedures for hearing test in detail in the method section. For example, how hearing was tested (facilities, testing equipment, methodology), how frequently it was performed, and, more importantly, what was the management strategies when hearing loss was found (stop the drug, reduce the dose, increase the dose interval, or retain current therapy while increasing the frequency of monitoring)?

Thanks for the suggestion. We have added this in the Methods section.

Abstract
The numbers of patients who completed their treatment and had a good outcome were inconsistent with those in table 1.

As indicated, this is an error and the discrepancies have been fixed.

Methods
Study population: What does mean "censoring"? (p4 line 7, p7 line 27, and table 2)

Please refer to our prior response in this regard.

Setting and procedure:

1) Add the method of drug susceptibility testing
As suggested, this has now been added reference 28-30

2) Add the reference to the WHO recommendation for amikacin dosage.
As suggested, this has now been added.
3) Add the policy and procedures for hearing test as mentioned above.
As suggested, this has now been added. See above addition, no 3.

Results
Cohort and study analysis
1) I hope the authors could provide clinical data briefly.
   - Drug resistance rate in the cohort, especially for AGs and FQs
   - Number of XDR-TB patients among the cohort
Thank you for the suggestion but unfortunately our dataset is limited in this regard.

2) Clarify the denominator in the analysis of treatment outcomes and proportion of good and poor outcome in total cohort, as described in the abstract.
We appreciate this suggestion; this is included in the statistical analysis section and table 1

p8. line 11 "Those with no documented hearing loss, treatment success was 60 (60%) whilst 29 (29%) were deceased." Why did the authors mention this sentence without mention of treatment outcome among patients with hearing loss? The authors wanted to show the poorer outcome for patients without hearing loss compared to those with hearing loss? However, it was not comparable because 40% of patients without hearing loss were still on treatment.

The Reviewer’s point is well taken. We have added that information to the line indicated by the reviewer. In addition, we have added the results of a sensitivity analyses aimed to show that the association remains present even after restricting the analyses to patients who had already finished treatment. However, as briefly discussed above, our main outcome is incidence of hearing loss. This implicitly assumes that the risk remains constant throughout the follow-up period. This point is now made explicit in the manuscript. In addition, our analyses accounts for time of treatment, decreasing the potential ascertainment bias mentioned by the reviewer.

Factors associated with amikacin-related hearing loss
- How many patients are tested with audiogram at baseline or during treatment?
Thank you very much, this is included in the text and table 1

Table 1.
1) Provide each data in 'lost to follow up' and 'failure' group.
   This has now been included in table 1

2) All abbreviations should be explained in a clear legend below the table.
   This has been fixed.

Table 2.
1) This table is simple comparison between the groups rather than multivariate analysis. I think “aOR(95% CI)” is typo.
Thanks for pointing out this discrepancy. It has been modified and the entire document has been revised for full consistency.

2) Are there any significant difference between patients with and those without hearing loss? It would be better to add p-value in the table.

We appreciate the Reviewer’s suggestion. However, we believe that the addition of p values to descriptive tables could be misleading due to potential imbalance when p values are not significant (because of small sample size) and balance when p values are significant (because of large sample size). In addition, the report of bivariate analyses is, by definition, confounded. Adjustment for these confounding factors is always required to obtain a better understanding of the differences between the groups under study (ototoxicity vs. no ototoxicity). However we would be happy to provide such information if the Editorial team and Reviewer think it is appropriate.

3) What does mean "censoring"?

Please refer to our prior response.

4) I think 'average' is an ambiguous term. Does it mean 'median' or 'mean'?

As suggested, we have changed average to mean throughout the document.

Table 3

1) 'Duration of amikacin treatment', 'average dose of amikacin', What is the referent? The referent groups must be made clear for the odds ratios presented. Without referent groups the odds ratios are not interpretable. I think it would be core data in the manuscript.

In all cases, the referent is the lack of exposure to the factor under analyses or the minimal value of the exposure. For dichotomic variables this is more intuitive (e.g. if only “male” is reported it is implicit that the comparison is “female”). For continuous variables the referent is the same but, perhaps, less intuitive. For example “average dose of amikacin” would be compared against the risk provided by the minimal average dose included in the analyses. The resulting ORs indicate a change in the risk given by each increase in the unit of measure (e.g. the OR of amikacin dose indicates the increasing risk of ototoxicity per mg/kg/month).

2) What does mean "predicts outcome perfectly"

When all participants who have a specific characteristic (or variable in the analyses) have or don’t have the outcome, it creates a “zero” value in the 2x2 table developed for its analysis. This is reflected as a “zero” denominator, making it impossible to analyse with the approach used for our study. A footnote explaining this point has been added to the tables.

Discussion

1. p10 line 2 "these recommended dosages may not apply to our population". It is hard for me to agree this sentence. Many factors including such as careful monitoring could be involved in ototoxicity.

As suggested, this phrase has been deleted. We agree with the reviewer. The relationships reported in our study are not causal and many factors could be confounding them. However, as the reviewer points
out below, we also believe that providing potential explanations for our finding is of major importance. Although our explanations remain speculative, they were based on the interpretation of our results in the context of physiological/biological plausibility and available data.

2. The authors need to expand the discussion on why the incidence of ototoxicity is much higher in their cohort and how to minimize it.

As suggested, this has now been added to the limitations section of the discussion.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests.