Author’s response to reviews

Title: Treatment outcomes and antiretroviral uptake in Multidrug-Resistant Tuberculosis and HIV coinfected Patients in Sub Saharan Africa. A Systematic Review and Meta-Analysis

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Author’s response to reviewer comments

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Elvis Dzelamonyuy Chem

c/o Public Health Institute

Faculty of Health, Education and Community

Liverpool John Moores University
Dr. Pedro G. Suarez
BMC Infectious Diseases
17/07/2019
Subject: Revision and resubmission of manuscript INFD-D-19-00981

Dear Dr. Pedro,

Thank you for your response to our manuscript submission and your interest in publishing it in BMC Infectious Diseases. We have revised the paper to reflect the reviewer’s helpful comments. We have also prepared a point by point response to each of the reviewer’s comments indicating how we addressed each concern. The revisions which have been approved by all co-authors are indicated in track changes within the revised manuscript attached to this email. We will appreciate a prompt reply from you at your earliest convenience.

Heterogeneity was correctly identified is an issue in this study by one of the reviewers. We observed that, this phenomenon was driven by the outlier study with very small size (Padayatchi et al 2014), explaining why we eliminated the study from the subgroup analysis by HIV status. However, so as to illustrate how all included studies contributed towards the study outcomes, we have included this study in the tables and forest plots. As we are concerned that removing studies to reduce heterogeneity could introduce bias into our estimates.

Sincerely

Elvis Dzelamonyuy Chem
Reviewer Comments, Author Responses and Manuscript Changes

Reviewer 1

Abstract

- Why only these three databases

Methodology

Line 83- why only these three databases

Response:

The databases used in search were chosen following consultation with a specialist librarian and a consideration of the focus of this piece of work - which was focused on clinical studies. Thus we focused on databases which are focused on clinical and health related areas, rather than those with a focus on social science. Test searches on a number of databases indicated that these three yielded appropriate citations. These database searches were also accompanied by searches of grey literature.

Line 103 - state that the studies had to have included HIV positive individuals, although not all participants had to be HIV positive. At the moment it reads as through all participants had to be HIV positive

Response:

This has been amended in the manuscript. Text now reads:

Included studies fulfilled the following characteristics: 1) Included culture or drug susceptibility testing confirmed MDR-TB patients

Lines 113- 119- can the authors describe how the retrieved studies were collated and duplicates removed. Was this done manually or a reference management software was used

Response:

This has been amended in manuscript. Text now reads:

After exhaustive database, bibliographic and manual searching, retrieved studies were screened with duplicates removed using the EndNote X8 reference management software.
Lines 137-138: why only 40 studies

Response.

There are concerns about the potential impact of using studies with small sample sizes particularly if these produce marked results in one direction or another. Our decision to use a cut off was based on the deliberations of the Cochrane skin group. One suggestion was not to include studies with <40 participants because of their impact on the overall weighting of studies in the review. We decided to use this as a cut off value for a good quality study, but included a study with a sample size of 23, which greatly affected the overall weight of our review during meta-analysis. https://skin.cochrane.org/sites/skin.cochrane.org/files/public/uploads/CSG-COUSIN_March%202015_M%20Grainge.pdf

lines 149-159: were descriptive statistics used to describe eligible studies. which parameters were used eg range, median or mean. Also what threshold for heterogeneity was used to determine whether a meta-analysis was necessary or not. Can the authors justify why they through a meta-analysis was necessary

Response: There was no coherence in the use of descriptive parameters within eligible studies. However, all studies reported the total number of participants which were collectively pooled and described as overall sample size and mean in line 173 under study characteristics.

Studies with I² >75% were considered heterogenous.

Reason for meta-analysis in midst of heterogeneity explained below

Results

for all the pooled estimates of the outcomes, can the authors report on the levels of heterogeneity found in the text of the results. The value of I-squared and the p-value would do

lines 213-216:

Response: The cure percentages reported in lines 213 – 216 are not pooled estimates. These are percentages per study that reported cure based on ART use (Table 1). There are no I² values for the table. No meta-analysis was computed in this case because of incomplete reporting and few studies in the table.

Could the lack of difference in cure by ART status be because the ART coverage was so high in all but one study.
Response: This could be the reason for the lack of a difference, however, the number of studies that reported complete data on cure was small. We are therefore cautious about drawing any conclusions.

Appendix 2

shouldn't the column on # and % on ART be labelled as the # and % of HIV positives on ART. At the moment it reads as if the denominator is all participants and not those on ART

Response: This has been amended in the table

Appendix 3: not clear who is included in this table. All MDR-TB patients or those co-infected with HIV. In the text, it seems this should be all MDRTB patients. What does summary refer to.

Response: This has been amended in the table. The first row in the table above the treatment outcomes, described included population. We have now transferred this to the title of the appendix.

Appendix 4 and 6: the authors show high levels of heterogeneity in the study level outcomes. Justify why you did a meta-analysis in the face of such high levels of heterogeneity

Response: Heterogeneity was clearly an issue in this study. We observed that, this phenomenon was driven by the outlier study with very small size (Padayatchi et al 2014), explaining why we eliminated the study from the subgroup analysis by HIV status. However, to illustrate how all included studies contributed towards study outcomes, it was included in tables and forest plots. We assumed eliminating studies to reduce heterogeneity could introduce more bias in our estimates. We have acknowledged the high heterogeneity in the limitations.

Reviewer 2

Muluken Melese (Reviewer 2): The article is well written and well analyzed. I do not have comments except on line 2014 to 2016. The "cure outcomes range from 22.2% to 57.7% among patients on ART and from the 28.6% to 54.7% among those not on ART medication" but in Table one the result is the reverse and please align the result of Table one with the text.

Response:
Uptake of ART for HIV did not affect the proportion whose MDR-TB was cured among the MDR-TB and HIV coinfected patients. Cure outcomes ranged from 28.6% to 54.7% among patients on ART, and from 22.2% to 57.7% among those not on ART medication (Table 1).

Thank you.