Author’s response to reviews

Title: ANTIRETROVIRAL THERAPY IMPROVES SURVIVAL AMONG TB-HIV CO-INFECTED PATIENTS WHO HAVE CD4+ T-CELL COUNT ABOVE 350CELLS/mm³

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Version: 2 Date: 29 Aug 2016

Author’s response to reviews:

The Editor,

BMC infectious Diseases,

We have responded to all the reviewer comments for our manuscript “ANTIRETROVIRAL THERAPY IMPROVES SURVIVAL AMONG HIV-INFECTED PATIENTS WITH TUBERCULOSIS AND CD4+ COUNT ABOVE 350 CELLS/mm³ (INFD-D-16-00303R1). Below is our point-by-point response to the comments:

REVIEWER #1.

Reviewer Comment:
Thank you for addressing the reviewers' comments. I am satisfied with the responses.
Author Response:

We would like to thank this reviewer for all their helpful and constructive suggestions to our manuscript.

REVIEWER #2:

Reviewer Comments:

Many thanks for this revision. Please find below a few responses in upper case letters. Overall, I feel there is a need to be more explicit in citing all the limitations of your analysis in the discussion.

Author response:

We would like to thank the reviewer for their comments. We have attempted to deal with their concerns and suggestions as best as we can in the below responses.

Reviewer Comment:

Methods

(1) Why wasn't BMI included as a variable in the models? Weight and height are routinely available in patient charts and published literature indicates it is a driver of mortality risk in people with TB. See:


PLEASE MENTION THIS AS A LIMITATION OF YOUR ANALYSIS.
Author Response:

We have mentioned this as a limitation to our analysis in the discussion, also citing the two studies mentioned by the reviewer (line 250).

Specifically, the sentence in the discussion that deals with this comment reads “Finally, previous studies have shown that weight and height are drivers of mortality in patients with TB[22, 23]. Although weight was measured regularly in the clinics, height was not, so we were not able to adjust for body mass index in the analysis”.

Reviewer Comment:

(2) Unclear whether model included time-updated CD4 cell counts or solely baseline value. Please clarify.

PLEASE MENTION THIS AS A LIMITATION OF YOUR ANALYSIS.

Author Response:

We have included a statement dealing with this limitation in the discussion (line 246).

Specifically, the sentence dealing with this reviewer comment reads, “As for information bias, we did not measure serial CD4+ T cell counts during follow-up, so we are not able to account for the time-dependent effect of the loss of cellular immunity as the CD4+ T cell count declined.”

REVIEWER COMMENT:

(3) Treating all LTFU as being alive and then as being dead are indeed the two extremes. But the reported values might be best to focus on an imputation based on published literature that has traced outcomes of PLHIV LTFU. See: Brinkhof MW, Pujades-Rodríguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS One. 2009 Jun 4;4(6):e5790. doi: 10.1371/journal.pone.0005790.

COULD YOU PLEASE PERFORM IMPUTATION AS A SENSITIVITY ANALYSIS AND REPORT THE RESULTS? UNDERSTAND THIS WILL LIKELY CHANGE EFFECT SIZE,
BUT THE DATA CONSISTENTLY SHOW THAT MANY PATIENTS LTFU ARE DEAD, PARTICULARLY AMONG THOSE WITH ADVANCED IMMUNOSUPPRESSION. IT IS DIFFICULT TO JUSTIFY IGNORING THESE DATA DURING THE ANALYSIS.

AUTHOR RESPONSE:

We appreciate the concern of the reviewer about the differential loss to follow-up, and we share that concern. With the suggestion of performing multiple imputations for survival analysis, we explored the literature in depth and discussed options with two biostatisticians, both of whom are experts in survival analysis. We found that multiple imputations for covariates is standardized and readily performed in survival analysis using available software. Multiple imputation of the outcome (i.e., date of death or survival) is not common and there are no standard statistical procedures for it. Both biostatisticians, and survival analysis theory, indicated that censoring of participants lost to follow-up is statistically robust, unless the individuals lost to follow-up have a different survival probability than the participants who remain in the analysis. It is for this reason that we performed the sensitivity analysis exploring the two extreme values for survival. We are confident that the true value lies between these two extremes. Moreover, since the effect of cART remained regardless of the scenario, we believe that the effect of cART is real, though we may not have estimated its effect precisely. We have mentioned this limitation in our discussion in line 245.

In this case sensitivity analysis is sufficient as an alternative to multiple imputations. We believe our analytic strategy adequately addresses bias which may arise from differential mortality in patients who are lost to follow up.

REVIEWER COMMENT:

Results

-Differences in follow-up. Cohort on ART followed approximately two years longer than cohort off ART. Do the data underestimate mortality rates in TB patients off ART? How was this managed analytically?

PLEASE MENTION THIS AS A LIMITATION OF YOUR ARTICLE.
AUTHOR RESPONSE:

Response:

We have mentioned this in the limitation section of our discussion (line 240) and further elaborated the problem of loss to follow-up in our discussion section. It is possible that the survival experience among those lost to follow-up differs from those who remain in care, though this cannot be verified empirically. To address the potential impact of follow-up bias, we explored the two extreme scenarios and presented the results under these extreme conditions. We believe that the true hazard ratio lies between these estimated extreme values. Moreover, since the 95% confidence interval excluded 1 in both scenarios, we infer a beneficial effect of cART.