Author’s response to reviews

Title: Predictors and outcomes of Mycobacterium tuberculosis bacteremia among patients with HIV and tuberculosis co-infection enrolled in the ACTG A5221 STRIDE study

Authors:

John A Crump (john.crump@duke.edu)
Xingye Wu (xwu@sdac.harvard.edu)
Michelle A Kendall (kendall@sdac.harvard.edu)
Prudence D Ive (pive@witshealth.co.za)
Johnstone J Kumwenda (jonnykumwenda@hotmail.com)
Beatriz Grinsztejn (beatriz.grinsztejn@gmail.com)
Ute Jentsch (ujentsch@cls.co.za)
Susan Swindells (sswindells@unmc.edu)

Version: 3
Date: 27 November 2014

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

Thank you for the opportunity to provide a revision of this manuscript. We have addressed each comment and suggestion of the editor and the reviewers. The specific nature of the response to each point is outlined with our submission and changes are made, where appropriate, in the revised manuscript text. This review has not been previously published nor is the manuscript under consideration for publication elsewhere. The authors have seen and approved the version of the manuscript enclosed and concur with its submission to BMC Infectious Diseases.

Thank you very much for considering this revision.

Sincerely,

John A. Crump, MB ChB, MD, DTM&H
Adjunct Professor of Medicine, Pathology, and Global Health
Division of Infectious Diseases and International Health
Duke University Medical Center
Reviewer 1

1. Comment. In the manuscript ‘Predictors and outcomes of Mycobacterium tuberculosis bacteremia among patients with HIV and tuberculosis coinfection’, the authors present the predictors and outcomes of Mycobacterium tuberculosis bacteremia among participants receiving baseline mycobacterial blood culture in an ACTG clinical study. Good outcome of patients with Mycobacteremia, with higher conversion rates and similar outcomes compared to patients without mycobacteremia. While these are good findings, some concerns should be addressed.

Response: The authors thank the review for the positive comments.

2. Comment: Major Compulsory Revisions. Page 6, line 17-20 'Mycobacterial blood cultures were not required by the protocol, were not standardized across sites, but were collected prior to the administration of tuberculosis treatment.' It remains unclear whether the patients in ACTG A5221 consented or they were re-consented for mycobacterial blood cultures.

Response: Yes, patients in ACTG A5221 consented for mycobacterial blood cultures. We have clarified this in the revision as follows ‘Mycobacterial blood cultures were not required by the protocol. However, all tuberculosis diagnostic information was required to be recorded by the study site. Mycobacterial blood cultures were not standardized across sites, but were collected at the discretion of the study team prior to the administration of tuberculosis treatment and were processed in laboratories adhering to Good Clinical Laboratory Practice standards.

3. Comment: Page 6, line 18-19 ‘Mycobacterial blood cultures were not standardized across sites…It would be good to give a brief description on how blood cultures were done and interpreted. The culture methods used, manual vs. automated systems. The volume of blood collected for culture etc. Since mycobacteremia is the main concept of this manuscript, consistency in the methods used across sites is vital.

Response: Unfortunately, we do not have information on how blood cultures were done at each site. The culture methods and blood volume were not collected in the clinical research forms used in ACTG A5221. There could be biases due to different laboratory techniques, and we have already made this clear in the text: ‘This analysis had a number of limitations…The use of mycobacterial blood culture during the baseline evaluation of ACTG protocol A5221 varied considerably by site and was at the discretion of the site team.’

4. Comment: Page 6; Since mycobacterial blood cultures were not part of the main study, at what point was blood collected? After starting ART or before? At what point did death occur?

Response: Blood samples were collected prior to or at study entry (randomization), with a median of 1.4 weeks before study entry. All samples were drawn before initiation of
antiretroviral therapy (ART) except two that were collected at the same day of the ART initiation. Deaths occurred after study entry from week 2 to week 20, with a median of 9 weeks after study entry. We had added that mycobacterial blood cultures were collected prior to ART initiation in the Methods section.

5. Comment: Minor Essential Revisions. Statistical analysis section; Consider mentioning the predictors as well as defining the outcome measure for the time-to-event in this section.

Response: The description of predictors has now been moved to the Statistical analysis section, as recommended. Furthermore, we have added the following sentence on the failure analysis methods: ‘Failure times were determined as the differences between randomization and failure dates or, if censored, last clinical visit dates.’

6. Comment. Page 8 line 9-10. The first statement is not clear. Consider a flow diagram showing how eligible participants were enrolled from the main studies. The total 88 and 90 participants is not clear.

Response: We thank the reviewer for identifying this. To make it clear we modified the sentence to: ‘Eighty-eight (97.8%) of 90 participants with baseline mycobacterial blood cultures were from sites in Rio de Janeiro, Brazil; Lilongwe, Malawi; and Johannesburg, South Africa. Among all participants from these 3 sites, those with mycobacterial blood cultures…’ We believe that the clarified text means that a flow diagram is unnecessary.

7. Comment: Page 8 line 16-18. Description on study sites should be under Methods section.

Response: We prefer to keep this in the Results section.

8. Comment: Page 9 line 1-7. This section should be under statistical analysis section.

Response: This section has been moved, as recommended.

9. Comment: Page 9 line 9. Consider clarifying the “0. 10 level. Also consider presenting results in sub-sections as bivariate predictors and multivariate predictors.

Response. We thank the reviewer for identifying this. We have changed the sentence to: ‘The covariates that were significantly (p ≤ 0.10) associated with higher odds of M. tuberculosis bacteremia were…’

10. Comment: Page 9, line 15-18, were these adjusted odds ratios? If so, consider mentioning so.

Response: This was mentioned in line 18. However, for clarity we have added ‘adjusted’ throughout.
11. Comment: Page 11 the subtitle should be discussion and not conclusions as it is currently.

Response: This has been corrected. There is now a separate Discussion and Conclusion section.

12. Comment: Line 13-16 should state that this was in agreement with the previous study otherwise the reference is not well placed.

Response. We thank the reviewer for identifying this. The reference has been moved and the result stated.

13. Comment: Page 16; consider revisiting references in line with the statements as they are phrased in the manuscript.

Response: This has been done.

14. Comment: The authors should consider continuous line numbering for quick reference during manuscript review.

Response: We apologize for not doing this.

Reviewer 2

1. Comment: There are no major compulsory revisions.

Response: The authors thank the review for the positive comments.

2. Comment: Minor essential revisions. Authors to clarify under the Methods section (first paragraph): at sites where mycobacterial blood culture were done- did all participants have procedure?

Response: No, not all participants from those sites did blood cultures. The collection of blood cultures was based on the site teams’ judgment. This point has been added to the Methods section.

3. Comment: Statistical review requested above for the following reason. The power to detect a difference between the groups is very low at 12% (as stated based on small sample size) but based on the very small number of patients with MTB bacteremia are the conclusions drawn sound?

Response: Yes. With such a low power, if no associations were found, we could not be confident to say there were no associations. Being aware of the limitation, we pointed out in the manuscript, ‘larger studies with standardized and consistent use of mycobacterial blood culture are needed to confirm the findings of our analysis.’
4. Comment: Discretionary revisions. Conclusions section to be separated into Discussion and Conclusion?

Response: We have now created separate Discussion and Conclusion sections, as suggested.