Author's response to reviews

Title: The complex relationship between human immunodeficiency virus infection and death in adults being treated for tuberculosis in Cape Town, South Africa

Authors:

Muhammad Osman (muhammadbinyusuf@gmail.com)
James A Seddon (james.seddon@imperial.ac.uk)
Rory Dunbar (rdun@sun.ac.za)
Heather R Draper (heather.r.draper@gmail.com)
Carl Lombard (carl.lombard@mrc.ac.za)
Nulda Beyers (NB@sun.ac.za)

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Author's response to reviews: see over
Dear Editorial Team,

We thank you for your careful consideration of our manuscript and we also thank the reviewers for their feedback. We respond to their comments below and the revised manuscript reflects the changes discussed and are marked in red for ease of review.

**Reviewer 1**

**Comment 1**
Unfortunately, it is difficult to say that the conclusions are adequately supported by the data – the author seems to be conflating an elevated risk ratio of mortality associated with HIV at a certain age or with a differing impact of HIV in different age groups. The statement “health systems need to focus attention on young patients with HIV, especially women, as they are at very high risk of death on treatment” implies that older persons are less likely to die from TB when in actuality, it just the gap in mortality rates between those dying who did and did not have HIV that is relatively smaller. In table 1, the authors clearly show that relative mortality rates for older persons are 21.1% (HIV+) vs 15.8% (HIV-) as compared to the rates among younger persons which were 4.4% (HIV+) vs. 0.9% (HIV-). This is logical as younger HIV-uninfected patients with TB are generally unlikely to die as they are easier to diagnose and tend to do well on treatment. Older HIV-uninfected patients with TB would be expected to have a higher mortality than younger patients (due to TB or other factors – clearly shown by the authors own RR of 9.16 for cases >65 years compared to 15-24yo) - thus the risk ratio between the HIV infected and uninfected in the older age group would be smaller, not because HIV has "less of an impact" in older people, but because the mortality rates in the comparison group (HIV uninfected) are higher at baseline. Also, it should be noted that many of the >65yo patients who died had an unknown HIV status (8.6% vs 3.7% in the 15-24yo).

**Response 1**
We thank the reviewer for these points and we agree that much of the effect for the increased RR between those with HIV and those without as patients get older is a function of an increasing risk of death in the HIV-negative group as patients get older. We have revised some of the language around this point and removed sections that state health systems should focus on young patients with HIV, especially women, as we agree this does suggest less focus on older patients where the risk is greater.

Having said this, we do feel that the elevated RR between those with HIV compared to those without in younger patients is important and should be dissected in more detail. These are patients who might be prevented from dying. To look at it another way:

With two equal-sized cohorts of 1000 older TB patients:
HIV+ 1000 of which 211 dies
HIV- 1000 of which 158 dies
Thus having HIV induces 53 ‘extra’ deaths
Thus of the 211 deaths, 53 are ‘preventable’ (25%)
With two equal-sized cohorts of 1000 younger TB patients:
HIV+ 1000 of which 44 dies
HIV- 1000 of which 9 dies
Thus having HIV induces 35 extra deaths
Thus of the 44 deaths, 35 are ‘preventable’ (80%)

Thus more extra death are seen in the older patients in absolute terms but the impact of HIV is more pronounced in the younger patients.

In terms of the older groups having a higher proportion of HIV-unknowns, this is an important observation and may have, to some extent, influenced results. We have commented on this in the discussion:

‘Although the number of patients with unknown HIV status was relatively small, the proportion was greater for older age-groups as compared to younger age-groups. It is possible that this may have influenced the perceived impact of HIV on death in different age-groups.’

Comment 2
Rather than suggesting that health systems focus more on younger patients rather than older ones, it would be more logical (and defensible) to emphasize that improved HIV prevention efforts could prevent deaths among young TB patients, as most young TB patients will not die during treatment except those who also have HIV. Also, one could use this data to point out the increase risk of death associated with HIV in patients with TB can be mitigated by ensuring that all patients with TB are tested for HIV and started on HIV treatment as soon as possible (ideally 2 weeks after starting TB treatment unless they have TB meningitis).

Response 2
These are excellent points and we have revised the article accordingly.
We have included the recommendations offered and focus on:
- Highlighting mortality in the younger is lower than the older but by eliminating HIV the risk of death in young TB patients is significantly reduced
- And that for overall HIV associated risk of death in TB patients – HIV status and early ART are beneficial

We have similarly removed this focus on young HIV-infected women from the abstract:

While mortality in the younger population is much lower than the older population, this study supports the implementation of HIV prevention interventions. Death among younger TB patients could be prevented as the majority of younger TB patients would not have died without HIV. For those diagnosed with TB, health systems need to focus attention on young patients with HIV, especially women, as they are at very high risk of death on treatment. Furthermore, the increased risk of death associated with HIV in patients with TB could be mitigated by knowledge of HIV status and early ART especially for those with low CD4 counts. require particular attention. A recent study demonstrated significant advantages associated with widespread implementation of WHO standards with improved outcomes when HIV-positive patients were started on ART early.
Comment 3
Additionally, the authors state that “it is satisfying to see a falling mortality rate during the four year study period” – however the data covers only a 3.5 year period because data in 2012 only go until June, therefore this year cannot be justifiably compared with the others. Furthermore, even if p values are provided to show that the decreased mortality is actually significant from 2009 to 2011, a drop in mortality from 5.5% to 4.5% could just be a fluctuation, and the mortality rate in 2012 could conceivably go back up if the full data for the year were available. Thus, I don’t think it’s reasonable to be very “satisfied” with this finding, although it is fair to present the data with the statistical analysis and hope that the trend continues downward.

Response 3
We describe the proportion of patients dying on TB treatment each year and carry out analysis to determine if these changes are due to chance or are statistically significant. In table 2 we have the calculated the RR for TB mortality per year including the 95% CI. The fact that final year only includes 6 months should not influence the analysis, other than that smaller numbers of patients will have led to wider confidence intervals. There is nothing to suggest that this is a fluctuation as it is a highly significant result. However, we have added a footnote to the table for clarity.

We do not think it would be valuable to attempt further analysis regarding changes over time as the inference will be limited; we feel that it would be more appropriate to include this in an analysis of the significance in the annual mortality rate change once reviewed over a longer period and have suggested this may be the focus of further studies:

While the study period is restricted to 42 months, a declining trend in annual mortality is observed and some of this effect may be due to a number of changes to cART policy in South Africa in recent years, with patients initiated onto cART at higher CD4 counts. It is important that this trend continue be measured and future studies should evaluate this over a longer duration.

Comment 4
The limitations of the work are stated relatively clearly, although the authors do not address the question of how their findings might have been changed if they were able to know the mortality rate among the patients who defaulted or were lost to follow up (neither the methods section nor Figure 1 show any patients being excluded for defaulting but the conclusions state that they were excluded).

Response 4
Patients who defaulted or were lost to follow up were classified as such, and they were included in the analysis as not having died. It is possible that some of these patients died but it is impossible to know this without tracing individual patients or comparing to death certification data. In the discussion, where we state that this approach excludes deaths occurring prior to treatment initiation and in those who have defaulted, we did not mean that these patients were actively excluded from the analysis. We meant that this type of study does not take that into account and therefore reflect the true mortality associated with TB. We have removed the word ‘exclude’.
We initially explored carrying out analysis of good outcome vs. poor outcome with poor outcome including death, default, failure and loss to follow up. We also explored looking at both death and poor outcome in only those with a known outcome. However, we felt that this much more extensive (and potentially confusing) analyses would detract from the main evaluation that we set out to perform, namely to assess the impact of HIV on death.

**Comment 5**
They authors also might have discussed the potential change in findings if they were able to know the HIV status of the patients whose status was unknown. Sensitivity analyses might have been helpful to address both of these questions, as both could have a significant impact on the findings presented and consequently the conclusions.

**Response 5**
In this study the proportion of those with unknown status was low at 3.1%. We have included an analysis of death in those with unknown HIV status in Figure 2 as well as describing the shape of the Kaplan Meier curve comparing the slope of those with HIV unknown to HIV positive/negative. We did explore carrying out a sensitivity analysis, by, in turn, excluding those with unknown HIV status and then in only those with known outcomes, but we felt that this would distract from the focus of this paper and add an additional level of complexity which may not add significant value to the findings we have highlighted.

**Comment 6**
Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes, although the references section needs a little attention (esp refs 2, 3, 13,17, 26 – missing full page refs)

**Response 6**
Thank you for these observations. We have edited the references stated. It should be noted however that for BMC journals and PLoS journals the articles do not have page numbers.

**Comment 7**
Do the title and abstract accurately convey what has been found? The title implies a level of “complexity” that I think is overstated in the conclusions (see major revisions above), and the abstract reflects this as well.

**Response 7**
While we would be comfortable excluding the word “complex” from the title we would request it be included as, even after the revisions have been incorporated as suggested above, we feel that there is complexity between HIV and TB which has been highlighted in this paper. However, we would be prepared to defer to the editor with regards the title.
Comment 8
Are the methods appropriate and well described? Yes, the methods are well-described, however, the authors do not describe how they classified patients who defaulted or were lost to follow up (included as alive?) and how many patients were excluded for lack of data.

Response 8
We hope this has been clarified in Response 4. All patients included in the TB register were included EXCEPT those under 15; those with MDR-TB and those at a military clinic.
Defaulted and LTF were not excluded from the cohort- here again a sensitivity analysis or imputation could have been employed but we felt was beyond the scope of this paper

Comment 9
Is the writing acceptable? The writing could use some grammatical editing for clarity but is overall acceptable.

Response 9
This has been noted. We have asked a number of non-author academic colleagues to review the article for clarity and have edited where this has improved flow.

Reviewer 2
We thank Reviewer 2 for assessing the article. We have not made any adjustments in response to these comments.

Additional Editorial Requests:
Comment 10
Copyediting: We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

Response 10
This has been addressed in response 9

Comment 11
Consent statement: Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.
**Response 11**

This has been included as requested

Ethical approval and a waiver of individual informed consent were received from the Stellenbosch University Health Research Ethics Committee (S12/01/018) and permission was obtained from the City of Cape Town Health Directorate.

**Additional comment:**

Please note in revising the manuscript we noted a calculation error in line 150. This has been corrected. Please note the calculation was stated correctly in Figure 1; table 1 and line 205 of the discussion.

Sputum smear results were recorded in 89.9% of all cases; HIV status could be determined in 96.9% of TB cases and of those HIV-positive, 94.6% had a CD4 count recorded. Of the 93,133 TB cases, 51,322 (55.1%) were male, 47,332 (50.8%) were HIV-positive and 4,619 (5.0%) died (Table 1).