Author’s response to reviews

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

Authors:
Simon Mutembo (simon.mutembo@gmail.com)
Jane Mutanga (mutangaj@uga.edu)
Kebby Musokotwane (kebymusokotwane@gmail.com)
Lutangu Alisheke (lalisheke@yahoo.co.uk)
Christopher Whalen (ccwhalen@uga.edu)

Version: 1 Date: 06 Jun 2016

Author’s response to reviews:

Response to Reviewer reports:

Reviewer #1: Thanks for the opportunity to review this manuscript addressing a pertinent question about the impact of timing of ART on mortality in HIV-TB co-infected patients with CD4 cell counts >350. It is a well written paper, and the authors have attempted to address inherent biases attributable to the retrospective nature of the cohort study design. However, my overarching concern with the manuscript is that the comparator group appears to be patients that have never started cART, rather than patients who started cART after completion of TB treatment. This would have been the better comparator group. There is also a lack of information on how the multivariable models upon which the conclusions are based were built, in particular if CD4 cell count was a predictor of mortality. More detailed feedback is presented below.

Response

We analyzed this program data with the aim of learning how cART affects mortality among HIV-TB co-infected patients with CD4+ cell count above 350 cells/mm³ when they are started treatment during cART or no cART at all or when cART is delayed until after TB treatment. However we were only able to find patients who were initiated on cART during TB therapy. Patients whose cART was differed were difficulty to track with a 24% lost to follow and 15%
transfer out to other facilities. Therefore our analysis could only be based on those who were started on cART during TB treatment and those who never started. Our findings are of significant public importance because not only do they demonstrate the beneficial effects of cART in this particular population but also they demonstrate the programming challenges and differential quality of care TB-HIV co-infected patients based on the cART treatment status. In response to critical an important comments from our reviewers we have added more detail on the model building, updated our results tables and responded to each concern below. Our analysis is interesting since it presents the real field experience.

Methods:

- Please state the exact period over which the data was collected, including the date at which subjects were censored

Response: Data was collected between January 2012 and June 2012. See line 76 in the manuscript.

- Please justify why data collected in 2006-2012 is only now being analysed and presented? Is more recent data available?

Response: The data was collected between Jan 2012 and June 2016 during a program activity to trace patients who lost to care. Although new data has accumulated over time, we would have to embark on similar activities to add the new data to this already existing data. We are working securing funding to carry out this activity and it may take time before all the information is available.

- Did TB diagnosis without micobiological confirmation fulfil the WHO criteria for smear-negative TB (e.g. have radiological/clinical evidence of TB and/or show a response to treatment)?

Response: All the case definitions were based on the WHO treatment guidelines and definitions. Therefore any patient who received a diagnosis of TB and was commenced on anti-tuberculosis treatment based on the national/WHO guidelines was regarded as a case of tuberculosis. Refer to line 90-93 for inclusion criteria which is based on the WHO guidelines line 101-103.

- Were patients’ in-patients or out-patients, or a combination of both? It was for both.

Response: Regardless of where you are seen from all hospitals maintain a single TB register, which has all the notified cases of TB.
In much the same way the all the cases of ART are maintained in the single ART register. Refer to line 89.

- Please describe the Zambia guidelines for timing of cART during TB treatment for the study period. We have included this part.

Response: Refer to line 97-104.

- Did the authors record data on whether those patients who initiated cART during TB treatment continued cART until censorship? - The authors report that the 'no cART' group never started cART (page 7, line 34). Were patients who started cART after TB treatment excluded from the study, or was this data not collected. It seems unusual to me that no patients were started on cART after TB treatment during the study follow-up.

Response: Yes in this paper this information is documented and the outcomes of all the patients who were initiated on treatment are recorded at the time of censorship [20 (25%) died, 19 (24%) were lost to follow up, 12 (15%) transferred out and 27 (34%) were still active in care at the time of censorship]. This information is summarized in figure 1. We also searched for data for patients who completed TB treatment without being commenced on cART. We found find records of 27 patients (34%) who were and yet not on cART. The speculation was that some of the transferred out patients were accessing treatment else where and so were the lost to follow up. However the aim of our study was not establish what has happened to this latter group of patients. We avoided dwelling much on this explanation since we do not have tangible evidence on which we can base our survival analysis.

Results:

- Please present data on all variables assessed for association with mortality, and how the final multivariable Cox proportional hazards model was generated. We have updated table 1 to include all the variables that were assessed in the Univariate analysis including those which were not statistically significant. We have also included a statement on how the final model was build. Refer to line 120-125.

- Is data available on the timing of cART during TB treatment and timing of cART (if started) in patients not receiving cART during TB treatment.

- Was CD4 cell count assessed as a predictor of survival? How often was CD4 cell count measured during follow-up? It seems to me that time-updated/current CD4 cell count during follow-up is likely to be an important predictor of mortality, even with the cohort all having CD4 cell counts >350. If not measured, please justify and add to limitations section.
RESPONSE

Data for the date of TB treatment initiation and cART intitiation was collected for both groups of patients. The whole of this survival analysis is based on these dates. However we were unable to collect data on time dependent CD4+ count. We have included the following explanation in the discussion section to address this limitation” In this study we were unable to collect serial CD4+ count for all the patients during their follow up in the cART clinic. CD4+ count is a time varying predictor of death especially in patients with lower CD4+ count below 350 cells/mm3. Even in patients with CD4+ count of more than 350 cells/mm3 we expect to see different survival patterns based on the change in the immune status as measured by CD4+ count”. See line 238 to 243.

- The duration of follow-up between cART and non cART patients appears to differ substantially. Was this all driven by mortality? Were the non-cART patients recruited at different time points during the long study period (e.g. the non cART patients all recruited at the end of the study period)? Did mortality rates differ by calender yea

response: It was most probably

Response:

The table below shows the number of patients in each cohort that were started on TB treatment. It is very unlikely that the patients in the no cART group were enrolled during the later times hence the short duration of follow up. The observation is likely to have been driven by mortality and loss to follow up (Overall 17% against 49%) . The observed recruitment in the table below does not have a pattern pointing to the point being raised by the reviewer.

<table>
<thead>
<tr>
<th>Year</th>
<th>Non cART</th>
<th>cART</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>2008</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>2009</td>
<td>18</td>
<td>68</td>
</tr>
<tr>
<td>2010</td>
<td>15</td>
<td>69</td>
</tr>
<tr>
<td>2011</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>2012</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>157</td>
</tr>
</tbody>
</table>
Discussion/Conclusion

The authors conclude that starting cART during TB treatment prolongs the survival of TB-HIV patients with CD4 count > 350. However, the comparator group in this study appears to be patients that did not start cART at all. I think the more pertinent question is whether cART prolongs survival of HIV-TB patients during TB treatment compared to patients who start on cART AFTER TB treatment completion. Can the authors present any data to address this question? If not, the objectives and conclusions need to clarify that cART during TB treatment only reduced mortality compared to no cART at all.

In my opinion, it is important that cART is included as a time-updated variable in an analysis with such long follow-up if available.

Response

We agree with this opinion unfortunately in our study we did not find patients who at the initial stage were treated for TB and started on TB after completing TB treatment. We can speculate that some of these patients may have gone to seek care at the facilities different from the facilities where they got the TB diagnosis and treatment. Hence the high rate of lost to follow up in this group. However this is a speculation we will have to investigate what happened to the patients who were lost to follow up. Did they go to die somewhere else to access treatment or are they still alive and yet not on treatment? It is important to answer these questions. However the objectives of our analysis cannot address these questions but addresses the pertinent question from a program point of view as to whether cART during TB treatment compared to no cART during this period affects mortality. In order to have clarity we have changed the wording as suggested by the reviewer. Refer to line 249 and line 253 in the conclusion section.

Reviewer #2: Introduction


Response: We have included this section. Refer to line 75

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:
Response: We would have liked to use BMI instead of weight. Unfortunately, although all the patients had their weight taken at the beginning of treatment and the follow up visits, the majority of patients both in the cART clinic and TB corner had no height measurements at all.

(2) Unclear whether model included time-updated CD4 cell counts or solely baseline value. Please clarify.
Response: We used baseline CD4+ count to estimate the Hazard of mortality. We have clarified this point in study population and discussion section

(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-Rodriguez 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.
Response: We did not use the imputation methods because the proportion lost to follow up was very high (8% in those on cART and 24% those not on cART). Our reasoning is that imputing for a high percentage of lost to follow up would most certainly result in creating a whole different data or analysis sample which will result in a different conclusion.

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?
Response: We recognize the fact that the median time to follow up for the 2 cohorts was different. However we assessed the distribution of the enrolments for the time of follow. The enrolment showed some form of uniformity between the groups. Therefore the difference in time
of follow up was driven by mortality and loss to follow which were significantly high in the no cART group.

Discussion


Response: We have included this.

---------------------

Editorial Requests
---------------------

Please note that all submissions to BMC Infectious Diseases must comply with our editorial policies. Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements this will cause a delay whilst the issue is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

Response: Done

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.
Response: Not Applicable

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

Response: Done

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

Response: Done