Reviewer's report

Title: Timing of treatment interruption among latently infected tuberculosis cases treated with a nine-month course of daily isoniazid: findings from a time to event analysis

Version: 0 Date: 07 May 2019

Reviewer: Joseph Puyat

Reviewer's report:

The manuscript examines the timing of and risks factors associated with LTBI treatment discontinuation in a US population. The manuscript's key findings include: 1) 47.9% of those who initiated LTBI treatment failed to complete therapy; 2) median time to interruption was 40.6 weeks; 3) about 4.7% quit therapy around after the first month; 4) pediatric patients, recent contacts, diabetics, HIV patients are less likely to quit, while African Americans and recent immigrants were more likely to stop treatment. Given the importance of the topic, the manuscript has the potential to contribute to the literature. However, the authors need to address a number of study design and analytic issues before the results can be considered for publication.

Below are the points the authors may wish to pay attention to in improving the manuscript:

1) The authors should clarify what they mean by this statement: "On average, patients defaulted on their prescribed nine-month daily INH therapy within the first month..." The data do not seem to support this statement.

2) The numbers mentioned in the text and on Figure 1 do not add up. From 19,726 a total of 992 who never initiated treatment were excluded. There should have been 18,736 in the next box but only 15,602 were shown. What happened to the ~3,000?

3) How were patients lost to follow-up differentiated from patients who chose to stop?

4) What is the rationale for considering losses at follow up as treatment default. Why are these events not right-censored?

5) Are adverse reactions and deaths constitute competing risks? If yes, why didn't the authors analyze these events as such?
6) Did any of the status pertaining to HIV, diabetes and other immunesuppresive conditions change during follow-up? If yes, why were they not examined as time-dependent variables.

7) There were a large number of patients excluded from the analyses. The authors did say (on the first paragraph of the Results section) that many of these excluded patients eventually completed therapy. Because of this, I would encourage the authors to examine more thoughtfully these exclusions as they could change the manuscript's key findings. For example, the statement on the abstract that: "Overall, 47.9% failed to complete therapy" is misleading as this appears to pertain only to about half of the total patients that could have been examined. Given these issues, I would hold off on interpreting or reading the rest of the results presented by the authors.

8) Figure 2 was hard to interpret. The y-axis should either say 0 to 100% or 0 to 1.00, not both. Also, I'm not sure if the authors are trying to show treatment discontinuation and not treatment treatment completion in these plots. As they are, the plots suggest that during the weeks before the fourth, 100% of the patients have completed treatment, which is not correct. Perhaps what the authors meant was that during the weeks before the fourth, all of the patients they examined have not discontinued treatment.

9) The authors mentioned in the text (and I think showed in Figure 2, as well) that the median time to treatment discontinuation was around 40 weeks. This is not possible if the authors excluded everyone with more than 9 months (~40 weeks) of treatment. I'd encourage the authors to review the design of their study and their data analysis.

10) Last, I would have appreciated more discussion of the authors' results. Most of the information contained in the discussion, while interesting, do not seem to be directly relevant to the study's key findings.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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