Author’s response to reviews

Title: The Effect of Incident Tuberculosis on Immunological Response of HIV Patients on Highly Active Anti-retroviral Therapy at the University of Gondar Hospital, Northwest Ethiopia: A Retrospective Follow-up Study

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Author’s response to reviews:

Dear Editors

The authors would like to thank the Editor and Reviewers for their careful review of our manuscript and providing us with their comments and suggestion to improve the quality of the manuscript. The main revised parts of the manuscript are highlighted and the following responses have been prepared to address all of the reviewers’ comments in a point-by-point fashion.

Editor’s comments:

The diagnosis of immunological failure is completely dependent on obtaining CD4 counts. Please add to the manuscript results the median number of CD4 counts obtained per patient. In addition, it would be helpful to know the proportion of failure patients diagnosed by each of the 3 WHO failure criteria. Also, you note several places and in particular the conclusion that the highest rate of immunological failure occurred at 6 months. You may want to qualify this statement somewhat, noting that you excluded patients with less than 6 months follow-up.

Response: The author really would like to thank the Editor for your salient observation. The median CD4 count is already reported. Immunological failure according to WHO failure criteria is also documented. As it is not possible to determine failure before the 1st appointment (6±2 months follow-up time) of the patients, excluded patients with less than 6 months follow-up couldn’t be consider.

Finally, you note a seeming discrepancy in your results in the association between incident TB and immunological failure between the multivariate Cox regression test (not significant) and the Kaplan-Meier log rank test (significant) (see discussion 3rd paragraph). It may be helpful to note that the log rank test is equivalent to the Cox univariate regression test. The multivariate Cox result would therefore be adjusted for the other significant variables included in the test and thus should be the "final" result. You should revise your discussion with this
in mind, emphasizing more the multivariate result and de-emphasizing the log rank test result. In this case, the association between incident TB and immunological failure is not significant (as defined by $P < 0.05$). You could add to your limitations that this result possibly could change with a larger sample size.

Response: The author completely agrees with editor’s comment and the document is modified as per your suggestion.

Reviewer: Dr. Brian Kigozi

Major comments:

Comment on Abstract:

1. Title: In the earlier version (3) the title used the phrase … “Patients on Highly Active Antiretroviral Therapy” which has been amended to “….Patients taking Highly Active Antiretroviral Therapy…” I suggest the authors use the former phrase.

2. Background: “Highly Active Antiretroviral Therapy (HAART)” is appearing. This is still interchangeably with “Antiretroviral therapy (ART)” throughout the abstract and manuscript.

3. Results: I suggest authors need to amend as follows…. “At multivariate analysis, Cox-regression analysis showed baseline CD4+ T-cell count <100 cells/mm³ (AHR 1.8; 95%CI: 1.10#2.92, p=0.023) and being male sex (AHR 1.6; 95%CI: 1.01#2.68, p=0.046) were found to be significant predictors of immunological failure. There was borderline significant association with incident TB (adjusted hazard ratio (AHR) 2.2; 95%CI: 0.94-5.09, p= 0.06). The risk of immunological failure was significantly higher (38.5%) among those with incident TB compared with TB-free (21.1%) (Log rank p = 0.036).

4. Conclusions: incident TB is not a major determinant of immunological failure as the null hypothesis is not rejected.

Response: The author completely agrees with reviewers’ comment and the abstract is modified as per your suggestion.

Manuscript:

1. Comments n the Introduction and Methods:

Reference no 8 should be cited as a website page in order to benefit the readers of the manuscript as the referred document is available on line. The document gives also various thresholds for HAART initiation;

- patients with CD4+ T-cell count of # 200 cells/mm³
- WHO clinical stage 3 with CD4+ T-cell count of # 300 cells/mm³ etc.

(Methods, study setting and population, 1st paragraph). I suggest “new active TB” should be replaced with “incident TB.”

Response: the reference is modified as per your comment. “New active TB” is also replaced with “incident TB.” The thresholds for HAART initiation is done as per WHO national guidelines. So, we done nothing about the thresholds for HAART.
2. Comments on Methods:

Study design and data collection: The following sentence is not clear and needs rephrasing as it appears as a prospective follow-up, “This period was selected to follow the patients for sufficient time.” Adult HIV patients……(having at least two CD4+ T-cell measurements). The word apart is missing. Similarly, the rest of the paragraph needs rephrasing to be more meaningful as it contains phrases like “…like the date ART was initiated…”, “All data needed for the study…”

Statistical Methods: Authors should mention the data software which was used for data entry and how it was exported to SPSS (version 20) for analysis. The word SPSS is appearing for the first time and should be spelt in full.

Response the comments about the methods: The author completely agrees with reviewers’ comment and the methods are modified as per your suggestion.

Comments on Results:

Baseline clinical characteristics of patients:
Second sentence I suggest the word “blood” is removed. The 3rd sentence the figures and percentages mentioned should be crosschecked with that derived from the table. Fourth sentence, percentages in brackets should come after the mentioned HAART regimens i.e stavudine/3TC/NVP or EFV (12.3%)…Reference should be made to Table 2).

Immunological failure after initiation of ART
3rd sentence: the median time from HAART initiation to immunological failure was 6 months. Authors should determine and compare the median time to immunological failure for patients with and without incident TB.

Figures 1-4: As in my previous report, y-axis should report the probability of immunological failure and x-axis report follow-up time in months.

Discussion: 3rd paragraph, 6th sentence. This sentence needs rephrasing and the following phrase removed, “…borderline association with…” Use of reference manager like endnote to organize references. Reference [24] cited before [23].

Response to comments about the results: The author completely agrees with reviewers’ comments and all the comments are modified as per your suggestion. However, regarding reference citation, reference [23] is already cited before [24] in the second paragraph of the discussion part.

Comments on Minor revisions:
Grammatical and spelling errors are still appearing in the manuscript. There is a need for proof reading by a person who comprehends and commands good English. Examples;
-introduction: 4th paragraph, first sentence: amend as …in TB/HIV co-infected patients….
-Methods:
Study setting and populations:
Hyphen between North and West and follow and up,
WHO national guideline should be amended to “WHO national guidelines”,
Ethical approval: Last sentence. “Individual records was coded and accessed only by research staffs.” This should be rephrased.
Results:
Baseline socio-demographic characteristics of patients: The 2nd last sentence needs correction and rephrasing. CD4+ T-cell counts should be reported as cells/mm³ throughout the manuscript and abstract.
Discussion: 3rd paragraph, 1st sentence. There should be no hyphen between the words Cox and regression.
Response to minor revisions-Thank you for your salient observation and the authors agree on the comments and the documents are revised accordingly.
Reviewer: Neil Martinson
Major compulsory revisions
1. Consider omitting Figure 1 or if you really want to retain it then the title of the Y axis on Figure 1 should be the same as the other figures, especially if it is exactly the same measure.
Response to Major compulsory revisions: the figure is used to show the cumulative/overall probabilities of immunologic failure. Therefore, the figure is modified as per your suggestion.
Minor Revisions
1. In the statistical section please make it clear that the covariables included in the model are baseline measures and not time updated.
2. Please request someone whose first language is English to proof read the manuscript.
3. In the limitations please expand on the point you make about virological measures not done and as a result that immunological failure could be related to viral resistance or non adherence.
Response to minor revisions: the authors would like to thank you for your salient observation and the authors agree on the comments and the documents are revised accordingly. However, concerning baseline co-variables, we already mentioned in the method parts.