Author’s response to reviews

Title: The effect of isoniazid preventive therapy on incidence of tuberculosis among HIV-infected clients under pre-ART Care, Jimma, Ethiopia: a retrospective cohort study

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Author’s response to reviews:

Reviewers Comments addressed point by point

1. Title
Rev comment 1: Title: It should be short. E.g. The effect of Isoniazid preventive therapy on the incidence of tuberculosis among HIV clients in Jimma, Ethiopia: Retrospective cohort study.
• The title was edited to make it short and informative.
• One author is added due to significant support in revising the manuscript.

Rev comment 2: Please review the results section in the abstract. E.g. ......And (AHR=3.16) is not clear.
• It was corrected in more clearer way

2. Introduction
Rev comment 3: The introduction is long, rambling, with some information being repeated and almost a list of statistics.
• Introduction part was reduced without affecting the important contents.

Rev comment 4: Please use recent literature on the burden of TB. Why do you use the 2011 estimate of TB where there is recent reports?
• The introduction was refined with 2013 global TB reports and recent studies

Rev comment 5: Please modify the last sentence of the introduction. E.g. the null hypothesis included...
• Modified and incorporated in the manuscript

Rev comment 6: Tuberculin skin testing (TST) status in Ethiopia
• What Ethiopian guideline says about Tuberculin skin test was incorporated in the introduction part of the manuscript.

Rev comment 7: Ethiopian’s Guidelines say about who should be put on IPT. I guess it’s quite important to understand those rules, in order to understand the
differences among those who took it and those who didn’t.

• The recommendation about IPT was addressed in the introduction part and
• Both groups of cohorts were similar in most of their characteristics except IPT status, both groups were eligible for IPT; however even though the non-IPT group patients are eligible to receive IPT due to different reasons they weren’t provided IPT.

3. Methods

Rev comment 8:- What method was used to sample the population and describe the catchment area for Jimma U Hospital?

• The technique used to sample the population and catchment area population of the study setting was described in methods part of the manuscript.

Rev comment 9:- Please describe in detail the number of the source population in each group. i.e. How many IPT users and non-users were there during the study period to take the required samples?

• Addressed in Sample size determination of method part

Rev comment 10:- The sample size estimates were taken from the first RCT of IPT, which was small study that showed a bigger effect of IPT than others - the assumptions should rather have been taken from the recent Cochrane review.

• The sample size estimate was taken from this study was because the background situation of the country was almost similar with resource limited setting like Ethiopia.

• In addition to the above point we have used adequate power and standard sample size formula

Rev comment 11:- Materials & Methods (2.7): when did time begin for follow-up of IPT users? Was it when they initiated IPT or when they completed IPT? Was time in the clinics prior to IPT included?

• TB free survival probability (survival analysis) was calculated in months using the time interval between dates registered on pre-ART care or IPT prophylaxis initiation to date of TB diagnosis or censoring.

Rev comment 12:- Materials & Methods (2.8): What software was used for the statistical analyses?

• Completed questionnaires were coded, entered and analyzed using STATA version 11.1 software

Rev comment 13:- There is inadequate description of the case definition of TB & how it was diagnosed in the study population, This is not described at all; neither is where the information was abstracted from. Was it from the hospital charts?

• The case definition and which group of patient were included in the study were addressed under Data processing and analysis part of the methodology. (Addressed in method part of the manuscript)

• Questionnaire was developed to abstract data from standard national pre-ART register, follow up forms and other clinical records. (Addressed in method part of
the manuscript)

Rev comment 14:- There is no such thing as an “unadjusted hazard ratio test”
• It was to say crude hazard ratio that was used to see the relationship between
  two variables without including other predictors, only to see the crude effects, replaced with crude hazard ratio.

4. Result

Rev comment 15:- In the results there is needless repetition of data in the tables & text, Please revise most of the sentences for clarity.
• The result part was minimized by only describing the important points.

Rev comment 16:- Please avoid describing “KM or multivariate analysis” again in the result section.
• Addressed

Rev comment 17:- For all data, I suggest a fixed number of digits after the decimal point. It’s better for reading and to remember the results while reading the paper.
• It was edited to make all numerical values to have fixed number of digits except P-value.

Rev comment 18:- when referring to a smaller number of subjects in a row, use "n" instead of “N”
• Addressed

Rev comment 19:- Results (3.1): provide median CD4 of entire cohorts and within each group
• Incorporated in the result part of the manuscript

Rev comment 20:- Some terminologies shall be defined in the text. E.g working and ambulatory Groups
• Already addressed

Rev comment 21:- The authors should consider also calculating an incidence rate ratio.
• Addressed in the result part of the manuscript

Rev comment 22:- The tables are mistakenly numbered and the reference to them on the text reflect those typos, I believe.
• Yes, already revised

Rev comment 23:- The inability to check on those lost to follow-up is really a problem in this study, because many of them could have developed TB and died from it.
• It was checked during analysis that there is no difference in demographic and pertinent clinical characteristics among lost to follow up patients with subjects under observation.
• A statistical and graphical test was used to assess the proportional hazard assumptions and the result showed that none of the predictors violated the proportional hazard assumptions and there was no strong evidence of non-fit. (addressed in method part and annex figure 2)

Rev comment 24:- The Cox analysis would benefit from a correlation evaluation between OI and WHO stages. I guess the same individuals would be in the same place, like presence os previous OIs correlates with WHO stages 3 and 4. If present, the multivariable analysis would allow only one of those 2 covariates.

• The model was checked for multicollinearity, and the VIF result was <10 which showed that there is no multicollinearity between the predictors. (Addressed in methods and table 6 annex).

5. Discussion

Rev comment 25:- The authors need to focus more on their point. The text comes and goes around the same references, and some allegation for differences found among the studies are not convincing.

• The discussion parts was edited to make more informative, and focus more on their points, it was reduced in a way it summarizes what was reported in result section and tried to synthesize the findings with previous studies. Comparison were made with published articles within the country.

Rev comment 26:- Discussion lack authority

• Discussion part was more refined with inclusion of authors

Rev comment 27:- Needs some language corrections before being published, Please avoid abbreviation for the first time. E.g. PLWHIV in the first sentence and AHR and PYO in the middle of the abstract, please avoid GC next to the year in all the text.

• The manuscript was corrected and edited for grammar, punctuation, first time abbreviation avoidance, avoid bullet points, and sentence structure.

Rev comment 28:- It should be revised again. It doesn’t follow the journal’s style.

• It was tried to follow strictly journals manuscript writing guideline with this revision

Rev comment 29:- The references are misplaced and many appear to be missing.

• Corrected accordingly