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:

Dear Editors:

BMC Infectious Diseases

Thank you for your consideration of the following original research article for publication:

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

The effect of Isoniazid preventive therapy among HIV-infected patients under HAART has been extensively studied on most countries of the world. But few studies have been done on the effect of Isoniazid preventive therapy in adult HIV-infected patients under pre-ART care in resource limited settings like Ethiopia. In spite of good evidence of IPT uses and the global recommendation, its coverage and implementation was very limited in the country.

Different studies conducted in different places had shown inconsistent results of the IPT protection against TB may cause further misunderstanding. Isoniazid preventive therapy effectiveness also varies with time and places and this necessitates having more local studies through critical review of barriers related to the health system, political system, and client related issues should be carried out in-order to develop nation specific strategies that are essential to foster the implementation of an IPT program.

In this research article, we analyzed the effect of IPT on the incidence of TB and determinants associated with TB disease among HIV positive patients (pre-ART) and Furthermore TB free survival probability in HIV infected patients among IPT user and non-users were specific objectives answered by this study.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. We hope that
the manuscript meets the high standards of your journal.
Sincerely yours.
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We have reviewed the above manuscript according to all reviewer's comments.

Author's response to reviews
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Version: 3
Date: 21 January 2015
Dear Taraz Samandari

Major Compulsory Revisions

1. Comment: The Introduction and discussion both lack authority: the Introduction is too long and almost a list of statistics; the Discussion does not synthesize their findings well with previous publications, many of these publications are not programmatic studies and therefore more appropriate to compare with this Ethiopian study.
   • Response: Introduction part was reduced without affecting the important contents. 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 programmatic studies. Comparison were made with published articles within the country. Discussion part was more refined with inclusion of authors.

2. Comment: Authors should indicate whether Ethiopia’s IPT policy requires use of the tuberculin skin test prior to initiation
   • Response: Ethiopian guideline recommendation with regard to tuberculin skin test was incorporated in the introduction part of the manuscript. (Page 4, last paragraph)

3. Comment: Materials and Methods: How TB was diagnosed is the critical measure. This is not described at all; neither is where the information was abstracted from. Was it from the hospital charts?
   • Response: The case definition and which group of patient were included in the study were addressed under Data processing and analysis part of the methodology. (Page 8, first paragraph)
   • Regarding the data from where it was abstracted there is a sentence saying “Questionnaire was developed to abstract data from standard national pre-ART register, follow up forms and other clinical records”. (Page 7, paragraph 2).

4. Comment: Materials & Methods (2.8): There is no such thing as an “unadjusted hazard ratio test”; this puts into question the authors’ statistical methods. This section needs to be reviewed.
   • Response: It corresponds to 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 in the manuscript (page 8, paragraph 2, line 8).

Minor Essential Revisions

Comment: Throughout the manuscript the authors would benefit from a review of grammar, sentence structure, use of abbreviations.
The manuscript was corrected and edited for grammar, punctuation, first time abbreviation avoidance, avoiding unnecessary bullet points, and sentence structure.

The manuscript has been edited by a native-English speaker with scientific expertise to improve the style of written English.

Comment: The initials “G.C.” appear in numerous places and should be removed
• Response: revised accordingly

Comment: The references are misplaced and many appear to be missing.
• Response: revised accordingly

Comment: Introduction: “related mortality and the risk of acquiring TB” should probably be “related mortality and the risk of incident TB”
• Response: correctly according to the suggestion (page 4, paragraph 2, line 3)

Comment: Introduction: Materials & Methods (2.1): describe the catchment area for Jimma U Hospital and population served
• Response: Catchment area population of the study setting was described in methods part of the manuscript. (Page 6, paragraph 2)

Comment: 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?
• Response: 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 (Page 8, paragraph 2).

Comment: Materials & Methods (2.7): What were the source records? Hospital paper charts?
• Response: Questionnaire was developed to abstract data from standard national pre-ART register, follow up forms and other clinical records. (page 7, paragraph 2)

Comment: Materials & Methods (2.8): What software was used for the statistical analyses?
• Response: Completed questionnaires were coded, entered and analyzed using STATA version 11.1 software (page 7, last paragraph)

Comment: “Table 5” is referred to in the text but I believe the authors intend “Table 4”
Response: Corrected

Discretionary Revisions

Comment: Results (3.1): provide median CD4 of entire cohorts and within each group
Response: addressed in result part (page 10, line 3)
Reviewer 2

Dear Gary Maartens

Comment: The introduction is long & rambling - suggest reduce by 50%. Importantly, it does not mention tuberculin skin testing, which is the major determinant of IPT success.

• Response: Introduction part was reduced without affecting the important contents.

Ethiopian guideline recommendation with regard to tuberculin skin test was incorporated in the introduction part of the manuscript. (Page 4, last paragraph)

Comment: What method was used to sample the population?

• Response: The technique used to sample the population was described in methods part of the manuscript (Page 7, first paragraph)

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

• Response: 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.

• The size of the sample be such that we may be ‘reasonably’ sure to achieve a statistically significant result if that clinically meaningful difference (or one even greater) really exists with adequate power and standard sample size formula, it isn’t necessary to depend only in Cochrane reviews.

Comment: There is inadequate description of the case definition of TB & how it was diagnosed in the study population

• Response: The case definition and which group of patient were included in the study were addressed under Data processing and analysis part of the methodology. (Page 8, first paragraph)

Comment: In the results there is needless repetition of data in the tables & text

• Response: The result part was minimized by only describing the important points.

Comment: The authors should consider also calculating an incidence rate ratio.

• Response: not clear since we have used adjusted hazard ratio.

Comment: The discussion should review their findings with those of the recent Cochrane review (no point in citing older meta-analyses) & of subsequent relevant RCTs

• Response: 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 programmatic studies. Comparison were made with published articles within the
country.
Reviewer 3
Dear Amare Deribew
Major revisions:
Comment: Methods
• 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?
• Response: Addressed in methods part of the manuscript(page 7, first paragraph)
Comment: Some terminologies shall be defined in the text. E.g working and
ambulatory groups
Response: Addressed (Table 2)
Comment: Table 5 is not included. Please include it with relevant information
such as numbers (%), and HR with 95% CI.
• Response: Mistakenly numbered as table 5 it was table 4 and corrected in this
revised version.
Minor essential comments:
Comment: 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.
• Response: Title change as suggested to “The effect of isoniazid preventive
therapy on incidence of tuberculosis among HIV-infected clients under pre-ART
Care, Jimma, Ethiopia: a retrospective cohort study”.
Comment: Please avoid abbreviation for the first time. E.g PLWHIV in the first
sentence and AHR and PYO in the middle of the abstract
• Response: Corrected in abstract and other section of the manuscript.
Comment: The objective needs modification: The objective of the study was to
compare the incidence rate of TB and identify factors associated with TB
development among HIV……
• Response: The objective in this study was to determine the incidence rate, to
determine the TB free survival time among both groups and identify determinant
factors for tuberculosis. (Page 2, introduction, line 5)
Comment: Please avoid GC next to the year in all the text.
• Response: Corrected
Comment: Please review the results section in the abstract. E.g. ……and
(AHR=3.16) is not clear.
• Response: corrected to make it clear (page 2, result, and line 7)
Comment: Introduction:
• Please use recent literature on the burden of TB. Why do you use the 2011 estimate of TB where there is recent reports?
• Response: We have updated the Background with more recent TB data. (Page 3, last paragraph)

Comment: Please use proper punctuation throughout the text. E.g in Ethiopia, the dual… In the country, 79%.....In Ethiopia, the effect (comma was missed). These are few examples but you have to revise it extensively.
• Response: corrected

Comment: Please modify the last sentence of the introduction. E.g The null hypothesis included…
• Response: modified as written in page 6, line 5 “The study was based on the hypothesis that there is no significant difference in TB incidence between IPT user and non-user among HIV-infected individuals”.

Comment: Methods:
• Please avoid bullet points throughout the text. E.g. Exclusion criteria included…
• Response: Corrected (study period and population, line 3)

Comment: Correct the use of unnecessary punctuations. E.g. Necessary information’s
• Response: re written as “Important data related…” Variables and source of data, line 3.

Also we have included variables collected by the study.

Comment: Please revise most of the sentences for clarity. E.g “Nearly half of the pre ART care receiving patients had at least one episode of opportunistic illness in the past; 45(49.49%) and 126(42.86%) of patients were from IPT and non-IPT group, respectively.” Could be written in a short and attractive form. There are several texts like the above, which needs extensive revision.
• Response: As suggested it was written as “Nearly half of the patients had at least one episode of opportunistic illness in the past, 145(49.49%) of them were from IPT and 126(42.86%) were from non-IPT group”. (Page 9, last paragraph) and other revision on sentence structure was also made.

Comment: Please avoid describing “KM or multivariate analysis” again in the result section. It was already mentioned in the methods. Directly put the findings. E.g Patients who didn’t receive IPT had……
• Response: corrected (Page 10, last paragraph)

Comment: Figure 1 should be revised to make it crystal clear. It is now blurred and very small. Please avoid the small title above the figure.
• Response: the figure is showing TB-free survival probability among both wings.

Comment: References:
• It should be revised again. It doesn’t follow the journal’s style.
• Response: With this version of the revision, we tried to follow strictly manuscript
writing guideline of the journal.
Reviewer 4
Dear Valeria Saraceni
Major compulsory revisions

Comment: Introduction: could be limited to 5 paragraphs, it's too long now, with some information being repeated,
• Response: Introduction and literature part was reduced without affecting the important contents. (Only eight paragraph for both parts with limited paragraph line)

Comment: Methods: It's not clear to the reader what the 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.
• Response: The recommendation about IPT was addressed in the introduction part (page 4, last paragraph) 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 due to different reasons they weren’t provided IPT.

Comment: suggest to the authors to add a chi-square test for homogeneity of proportions, so the readers can better assess the differences among IPT users and non-users - Tables 1 and 2 will benefit from that. (Tables 1 and 2 would benefit from a column with the resulting p-value of the chi-square for homogeneity of proportions. I suggest taking out the TOTAL column and add the p-value).
• Response: It was good suggestion but we had used crude Hazard ratio which was more essential than the chi-square test that to illustrate both the association and direction of relationships.

Comment: Results: 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.
• Response: It was edited to make all numerical values to have fixed number of digits except P-value.

Comment: when referring to a smaller number of subjects in a row, use "n" instead of "N".
• Response: corrected

Comment: The tables are mistakenly numbered and the reference to them on the text reflect those types, I believe.
• Response: corrected

Comment: 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 vs previous OIs correlates with WHO stages 3 and 4. If present,
the multivariable analysis would allow only one of those 2 covariates.

- Response: 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).

Comment: Discussion
The authors need to focus more on their point. The text comes and goes around the same references, and some allegations for differences found among the studies are not convincing.

- Response: 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.

Comment: The discussion around CD4 cell counts on page 11 is confusing and didn't add new information from this study.

- Response: revised accordingly (page 13, line 17)

Comment: 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.

- Response: 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 (i.e. CD4 count, WHO stage, IPT use, age, sex etc.).

- 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)