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

Authors:

Lelisa Fekadu Assebe (lelfekadu1@gmail.com)
Hailemariam Lemma Reda (hailelm@gmail.com)
Alem Desta Wubeneh (alemdw@gmail.com)
Wondewossen Terefe Lerebo (darfiroerjabo@yahoo.com)
Saba Maria Lambert (Sabalamberg@hotmail.com)

Version: 5 Date: 22 March 2015

Author’s response to reviews: see over
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.

Lelisa Fekadu (corresponding author)
Address: Ethiopian Federal Ministry of Health, Disease Prevention and Control Directorate, Addis Ababa, Ethiopia
E-mail: lelfekadu1@gmail.com
Phone: +251-922-914132
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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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Reviewer

Dear Taraz Samandari
Commented on Pdf document of the manuscript
Abstract part
Comment: Revise the sentence “HIV patient” to “HIV patient” “crude effect of both groups” to “crude effect in both groups” “Cox” to “A Cox”
Response: - Change made as indicated by the reviewer (page 2)

Comment: conclusion: Because of the type of study, the authors cannot make such a statement implying causality. Just that "IPT was associated with a twofold reduction in TB." The second sentence is appropriate but redundant.
Response: - It was corrected as “IPT use was associated with fifty percent reduction in new cases of tuberculosis and probability of developing TB was higher in non-IPT group”

Discussion
Comment: Discussion: 1st paragraph “3.78 is higher than 2.6. Therefore this part of the statement seems incorrect”
Response: - corrected (Page 10, last paragraph)

Comment: Discussion: mention the rationale in the first paragraph “additionally the other studies had at least some of the populations using ART, whereas no one in JUSH was receiving ART”. That should be mentioned here.
Response: - The reviewer is correct and we have added this sentence to the discussion

Comment: Discussion: this sentence “This difference might be explained by limited scope focusing only to see incidence of pulmonary tuberculosis cases in Thailand study” was unclear.
Response: - because they try to analyze only focusing on those who develop lung tuberculosis

Reference
Comment: unable to find reference number 18.
rate among HIV-infected adults enrolled in HIV care in northern Namibia 2012: a retrospective cohort study. AIDS 2012, Abstract no. WEPE066.” And
The result of this article “1115 individuals were included in the analysis, and followed for 3770.8 Person-Years (P-Y). 67.3% were females, 82% on ART and 36.2% completed six months of IPT. Overall, TB IR was 2.3 per 100 P-Y. TB IR was 3.07 per 100 P-Y in the unexposed group and 1.14 per 100 P-Y in the exposed group (HR 0.38; 95% CI, 0.22-0.65;P=0.0004). After adjustment for confounding effects of gender, weight and WHO Stage of HIV disease, HR was 0.52 (95% CI, 0.28-0.95;P< 0.0001). ART, CD4 count and age were found to not be confounders”.
Response: - Change made as indicated by the reviewer (page 20)
Annex
Comment: figure 2 need label for y axis.
Response: - we have deleted this figure as indicated by the other reviewer it wasn’t belong to main manuscript.
Reviewer
Dear Gary Maartens
Comment: The authors have not addressed my comments on the introduction - it is still far too long & they persist with citing old meta-analyses rather than just the 2010 Cochrane review. Although they have added that TST is not a requirement in Ethiopia (which belongs more in the methods) they have failed to summarize the evidence from the meta-analysis that IPT is only significantly effective in TST+ people.
Response: - Regarding recommendation of national guideline about TST we have now included this sentence in the methods section as the reviewer indicates (page 7, last paragraph)
Evidence from the Meta analysis was summarized as “Meta-analyses of randomized controlled trials have shown that IPT reduces the risk of TB by 33% overall and by 64% when targeted to HIV infected individuals who had a positive tuberculin skin test” (page 4, last paragraph).
We have reduced the introduction to the maximum as possible in this version.
Comment: The authors have also still not given the breakdown of TB diagnosis as requested ("how [TB] was diagnosed in the study population”)
Response: - In the Methods section we have elaborated how TB classification was made in this study (page 7, first paragraph)
Comment: Finally I requested an incidence rate ratio, which the authors rebut by saying they have given an adjusted hazard ratio, which is not the same.
Response: - we apologize for the inconvenience we are not clear on which part of the section (is that multivariate analysis part) that you requested an incidence rate ratio.
Reviewer
Dear Amare Deribew
Minor essential revisions:
Introduction:
Comment: Globally, According to ….needs revision on use of capital letter. There are many similar errors throughout the text
Response: - corrected accordingly (page 3, last paragraph)
Comment: This report also shows: ....needs revision. This is a new paragraph and please don’t refer ‘this report”
Response: - corrected
Methods:
Comment: Please revise the following sentence which is not correct and attractive: Baseline CD4+ cell count, baseline weight….. (…. Time to new cas of TB)
Response: - Revised accordingly throughout the manuscript
Results and methods:
Comment: Please avoid the study subjects and replace it with study participants
Response: - corrected accordingly (page10, third sentence and table 1, 2)
Comment: The effect of IPT on TB development was mentioned several times. See the subtitle predictors of TB. Please avoid repetition of the same ideas
Response: - repeated sentence under predictors of tuberculosis was omitted
Comment: The conclusion should be short based on the major findings.
Response: - we have already revised our conclusion and recommendation part through summarizing the major finding from the result part.

Reviewer
Dear Valeria Saraceni
Minor Essential Revisions:
Comment: P.11 - the 2nd paragraph starts with the same sentence that is the first paragraph under Predictors of tuberculosis incidence.
Response: - Repeated sentence under predictors of tuberculosis was omitted
Comment: This very section would benefit of a concise description of the findings in the multivariate analysis.
Response: - we tried to make multivariate analysis interpretation shorter and clearer tried to put the summary of multivariate analysis (page 11).
Conclusions and recommendation:
Comment: The authors could summarize their main conclusions without repeating their findings here.
Response: - we have already revised our conclusion and recommendation part through summarizing the major finding from the result part.
Tables:
Comment: I see no need for the inclusion of Tables 5 and 6. Figure 2 doesn't belong to the main paper.
Response: - Removed, including figure 2