

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Determinants for tuberculosis in HIV infected adults in Northwest Ethiopia: a multicenter case control study
AUTHORS	Alemu, Yihun Mulugeta; Awoke, Worku; Annelies, Wilder-Smith

VERSION 1 - REVIEW

REVIEWER	Shallo Daba Hamusse Oromia Regional Health Bureau, Ethiopia, Addis Ababa
REVIEW RETURNED	04-Jul-2015

GENERAL COMMENTS	<p>General comments;</p> <p>I have read the article " Determinants for tuberculosis in HIV infected adults in Northwest Ethiopia: a multicenter case control study" with great interest.</p> <ul style="list-style-type: none">• The abstract: the abstract is well written, clearly defining the objective of the study, presenting relevant results with data supported conclusion.• The introduction provides the rationale for undertaking the study and it is well written and coherent.• References are up to date <p>Major compulsory comments</p> <p>Methods</p> <p>METHODS</p> <p>1. The Authors select controls HIV infected adults without active TB, However, it is good to describe if control participants have been screened for TB to rule out that they had no active TB. It is imperative to screen HIV positive individuals for TB in order to rule out they had no active TB. Therefore, I suggest to describe in the method their screening procedure if they were screened or describe as limitation of the study if they were not screened .</p> <p>2. Although active TB diagnostic guidelines in Ethiopia includes sputum microscopy ,culture, molecular, histopathology and radiological examinations, except sputum microscopy all are not available at health center level. However, authors included ten health-centers in the study where there is no culture, molecular, histopathology and radiological examinations facilities. Thus, I suggest to clearly present the diagnostic methods used to diagnosis active TB cases both at hospital and health center other than presenting what is in the guideline.</p> <p>Result</p> <p>1. Table 1. The value under kappa in the yes row of case column is missed</p>
-------------------------	---

	<p>2. Table 3. Why 22(14.7) active TB cases who were diagnosed as active TB patients were taking IPT ?</p> <p>Discussion</p> <p>1. In most parts of the country ,people who chewing khat are usually chewing in group either with their family members (house hold members) or with other friends who are not house hold members. Hence, there a chance of spreading the diseases to other people who were not family members or acquiring the diseases from someone who is not a house hold members. therefore, the Authors should also consider close TB contacts not only family history of TB contact as a risk factor for TB . Otherwise need to describe as limitation .</p> <p>2. These host related variables (cigarette smoking, khat chewing and alcohol consumption) are very sensitive for some people to disclose. Of course those with active TB cases may disclose as they may thought if they disclose will get better treatment where as those without active TB may not disclose. Therefore, don't you think of information bias? I think it is also good describe as a limitation of the study.</p>
--	--

REVIEWER	Yadeta Dessie Haramaya University Ethiopia
REVIEW RETURNED	25-Jul-2015

GENERAL COMMENTS	<p>Major comments</p> <ol style="list-style-type: none"> 1. The rational of the study was not well explained in to the context of Ethiopia. There are significant number of studies which address the topic in the country therefore, the authors need to exhaustively show the gap of the existing studies. In the same line what is the specific aim of this study as almost many of these determinants are identified and reported already. Do the authors expect context variations for these determinants? What 'active TB' means in this study? The definition of this is mandatory to be explicitly presented. For example, if the patient had already developed TB and started ART, how this was managed in the case selection? 2. In the study, the substance use timing was not clear, which mean weather the alcohol consumption, smoking and the khat chewing takes happening during the study period 3. The authors stated that they considered the health facilities based on the adequacy of TB cases. What does it means? Were there other health facilities which you excluded from the study having TB cases? If that is the
-------------------------	--

	<p>case, don't you think it can introduce bias due to not including them?</p> <ol style="list-style-type: none"> 4. As the lack of causality was stated as limitation, the word 'determinants' use in explaining the factors is not logical as to me. In the result section the author used the factor associated vs determinants interchangeably many times. In the same line, some of the explanations in the results and discussion sense causality concept. For example on line 27 of the result part it was stated as 'those houses having separate kitchen were more likely to develop TB' 5. The number patients (both on ART and not initiated ART) in each health facilities need to be presented in order to show how many are represented from each facility. <p>Minor comments</p> <ol style="list-style-type: none"> 6. What were the other criteria that made the health facility selection purposive apart from the number of cases? 7. Was study matched or unmatched case control? 8. Exclusion and inclusion in regard to the record for the study is needed as the secondary data source is usually characterized with the incomplete data? 9. What are residential officers mean in this study context? 10. IQR is usually presented with median while SD is with mean. The authors here used mean with IQR which is not common. Did they check age distribution (as skewed versus normal)? so that it is possible to identify whether to apply a mean or median? 11. One of the cells under Khat chewing bivariate analysis result was incomplete - the authors need to check this. 12. The time period/time of the 'use substance' was not clearly shown. Is that current/during the data collection history or the past history? 13. The funding source of the study neither was nor reported and it is preferable, if the author included under
--	--

	<p>acknowledgment of the study/ or elsewhere?</p> <p>14. The conclusion part overlooked the substance use in the main body of the manuscript while it has been presented boldly in the abstract section. I would normally expect the conclusions in the main body need to be comprehensive than the one presented under the abstract.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer one: comment and answer

Methods

1. The Authors select controls HIV infected adults without active TB, However, it is good to describe if control participants have been screened for TB to rule out that they had no active TB. It is imperative to screen HIV positive individuals for TB in to order to rule out they had no active TB. Therefore, I suggest to describe in the method there screening procedure if they were screened or describe as limitation of the study if they were not screened.

→ Controls had been screened for TB and active TB was ruled out. The screening procedure include: the patient was asked for four symptoms at each visit (cough, weight loss, night sweating or fever). If the patient presenting with any one of the symptoms this patient is TB suspect or screened positive and should be evaluated for TB by the TB diagnostic tools.

2. Although active TB diagnostic guidelines in Ethiopia includes sputum microscopy, culture, molecular, histopathology and radiological examinations, except sputum microscopy all are not available at health center level. However, authors included ten health-centers in the study where there is no culture, molecular, histopathology and radiological examinations facilities. Thus, I suggest to clearly present the diagnostic methods used to diagnosis active TB cases both at hospital and health center other than presenting what is in the guideline.

→ In hospitals, sputum microscopy, histopathology and radiology examinations are used as the TB diagnostic tools. In health centers, sputum microscopy is the main stay of TB diagnostic tools and patients will be sent for other diagnostic evaluation to hospitals and private institutions where the diagnostic tools are available.

Result

1. Table 1. The value under khat in the yes row of case column is missed

→ Missed data in table one is now included

2. Table 3. Why 22(14.7) active TB cases who were diagnosed as active TB patients were taking IPT?

→ Those patients were took IPT in the past(1st) but they develop active TB(2nd) i.e. patients with history of IPT in the past but the IPT was not prevent the active TB / Even though they took IPT they were diagnosed with active TB.

Discussion

1. In most parts of the country, people who chewing khat are usually chewing in group either with their family members (house hold members) or with other friends who are not house hold members. Hence, there a chance of spreading the diseases to other people who were not family members or acquiring the diseases from someone who is not a house hold members. Therefore, the authors should also consider close TB contacts not only family history of TB contact as a risk factor for TB. Otherwise need to describe as limitation

→ Tuberculosis has a possibility to spread to other people who is not a household member. But this study was considered, only family members were close tuberculosis contacts. This is reflected in the limitation part of revised manuscript.

2. These host related variables (cigarette smoking, khat chewing and alcohol consumption) are very

sensitive for some people to disclose. Of course those with active TB cases may disclose as they may thought if they disclose will get better treatment where as those without active TB may not disclose. Therefore, don't you think of information bias? I think it is also good describe as a limitation of the study.

→ Information bias in relation to substance use is now reflected in the limitation part of the study.

Reviewer 2

Major comments and answers

1. The rational of the study was not well explained in to the context of Ethiopia. There are significant number of studies which address the topic in the country therefore the authors need to exhaustively show the gap of the existing studies. In the same line what is the specific aim of this study as almost many of these determinants are identified and reported already. Do the authors expect context variations for these determinants?

→ Rational of the study in context of study settings is reflected in the revised version of the manuscript. Determinants for tuberculosis among HIV-positive adults vary from one setting to another. Therefore, a context specific study in a high burdened TB/HIV region indicated.

Example: the independent association of life style variables (Khat chewing and tobacco smoking) have been rarely identified in this types of source population (HIV infected adults).

What 'active TB' means in this study? The definition of this is mandatory to be explicitly presented.

For example, if the patient had already developed TB and started ART, how this was managed in the case selection?

→ Active TB is defined as patient who is diagnosed with TB by one or more of TB diagnostic tools (sputum microscopy, x-ray, histopathology, culture or molecular).

→ ART is not a criteria for selection of cases or control. Cases and controls were selected based on the TB status. Cases were HIV patients with TB while controls were HIV patients without TB. (This has been elaborated further under "Methods: Participants" section).

2. In the study, the substance use timing was not clear, which mean weather the alcohol consumption, smoking and the khat chewing takes happening during the study period.

The definition of substance use is now reflected in the revised version of the manuscript, including the timeline used to define substance use. A person with substance use (either chewing Khat, consuming alcohol or smoking) was defined as an individual who is currently using the substance or has a history of substance use.

3. The authors stated that they considered the health facilities based on the adequacy of TB cases. What does it means? Were there other health facilities which you excluded from the study having TB cases? If that is the case, don't you think it can introduce bias due to not including them?

We do not considered the health facilities based on the adequacy of TB cases. We actually assessed the adequacy of TB cases to decide how many health facilities are required for our calculated sample size. We do not exclude health facilities from the study having TB cases. The detailed sampling procedure is reflected in the revised version of the manuscript. A total of fifty-two health institutions are providing HIV care service in 44 districts of Awie, West Gojjam and North Gondar Zones. Ten districts were randomly selected and all health institutions in the ten districts were included in the study. Three hospitals and ten health-centers were included.

4. As the lack of causality was stated as limitation, the word 'determinants' use in explaining the factors is not logical as to me. In the result section the author used the factor associated vs determinants interchangeably many times. In the same line, some of the explanations in the results and discussion sense causality concept. For example on line 27 of the result part it was stated as ' those houses having separate kitchen were more likely to develop TB'

Our study has limitation of causality because it was retrospective case control study, it does not establish temporal relationship. The word determinant is more appropriate for retrospective case control study. It shows how the evidence is stronger (has comparison group) than the term "associated factor" 'mainly the term used for cross-sectional study. Using the term "associated factor" as determinant is corrected. The word "more likely" is not mean to use for causality concept or for study which establish temporal relationship would rather use for the study that evidences are stronger

(has comparative group). To indicate the temporal relationship/ causality concept for example 'prospective cohort' or 'prospective case control' use the word " risk factor".

5. The number patients (both on ART and not initiated ART) in each health facilities need to be presented in order to show how many are represented from each facility.

In our study, ART is not the outcome variable; rather it is one of the exposure variables and it was not our intention to identify differences between the 13 health institutions. Hence, we did not think it was necessary to present the number of patients (based on ART initiation) as a Table in the manuscript. However, if the editor is interested in such an analysis, we would be happy to provide it.

Minor comments and answers

6. What were the other criteria that made the health facility selection purposive part from the number of cases?

Explained in question number 3.

7. Was study matched or unmatched case control?

This is an unmatched case-control study.

8. Exclusion and inclusion in regard to the record for the study is needed as the secondary data source is usually characterized with the incomplete data?

The data were collected by conducting interviews and by using data extraction tools from patient's registration profiles. For secondary data source, the follow up variables (ART, IPT, and INH) are refilled every month when the patient comes for ART, the base line variable such as CD4 count is recorded at the time of enrollment to an HIV care clinic. For those variables incomplete data were rare. Therefore, we do not use incomplete data as exclusion criteria.

9. What are residential officers mean in this study context?

The word "Medical officers " means "Health Officers"

10. IQR is usually presented with median while SD is with mean. The authors here used mean with IQR which is not common. Did they check age distribution (as skewed versus normal)? So that it is possible to identify whether to apply a mean or median?

The age distribution has shown skewness. Therefore, median is included instead mean. This is now reflected in the revised manuscript under the results section.

11. One of the cells under Khat chewing bivariate analysis result was incomplete - the authors need to check this.

Incomplete data for the variable Khat is now included in the revised manuscript.

12. The time period/time of the 'use substance' was not clearly shown. Is that current/during the data collection history or the past history?

The timing of substance use is included in the revised manuscript and also has been addressed in Question 2.

13. The funding source of the study neither was nor reported and it is preferable, if the author included under acknowledgment of the study/ or elsewhere?

Funding source is included under the acknowledgements section in the revised manuscript.

Funding: PAGEL (Partnerships for the health sector in developing countries offers German institutions of higher education many different opportunities for international cooperation related to the health sector in developing countries) funded this article. The points expressed in this article are the responsibility of authors, do not reflect the view of PAGEL. The funding source had no role in design, analysis, wrote paper, manuscript preparation or decision for publication.

14. The conclusion part overlooked the substance use in the main body of the manuscript while it has been presented boldly in the abstract section. I would normally expect the conclusions in the main body need to be comprehensive than the one presented under the abstract.

The conclusion has been revised to be more comprehensive in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Shallo Daba Hamusse Head, Oromia Regional Health Bureau
REVIEW RETURNED	09-Nov-2015

GENERAL COMMENTS	<p>General Comments</p> <p>The authors are incorporates pervious comments and have significantly improved the quality of the manuscript. Now I have very few and minor comment to be incorporated before publication.</p> <p>I. Abstract</p> <ul style="list-style-type: none"> - under line 42 it is good if "isoniazid(INH) therapy" written as isoniazid preventive therapy (IPT) - "INH therapy" at line 51 should replaced with IPT <p>II. Introduction</p> <p>The abbreviation at line 5 "HIV" is well known it need to write in full word first and then use the abbreviation in the rest of the paper.</p> <p>III. Methods</p> <ul style="list-style-type: none"> -The word "provinces" in line 42 is not known in Ethiopia and not clear if it mean zone or district. Therefore, it is good to replace with the word District to avoid confusion. -Page 6 line at 12, "at" need to replaced by to (at hospitals replace by to hospitals) <p>IV. Result</p> <p>In the result line 25-27 the authors describe as follow: "The bivariate analysis showed that male patients (COR (crude odds ratio) =1.48; 95% CI: 0.99, 2.12; p-value = 0.053) were more likely to have tuberculosis compared to female patients". However, the association is not statically significant see the 95%CI (0.99-2.12) has included included 1, which means the association is not statically significant. Therefore, the association is by chance. I suggest to remove the "more likely to have tuberculosis" or the authors should rewrite as follow - Although, in bivariate analysis male patients had 1.48 times more likely to have TB compared to female patients, the association is not statically significant.</p> <p>V. Discussion</p> <p>Page 13 Line 29-31 : When compared with female HIV positive adults, we found that male HIV positive adults were more likely to develop TB. Men are reported to be more susceptible to tuberculosis infection. I think the association between male sex and TB infection among male patients who have HIV infection is not statically significant even in the bivariate analysis . The association is mainly due to chance (95%CI) include 1 which showed t no statically difference between male and female. The Authors may discuss in the other way round which means indicating no association between HIV/TB infection and sex difference and discuss what it mean comparing with other similar studies. Otherwise, good to remove this sentences.</p> <p>-In most of discussion part the authors use " literature" elsewhere. I think it good to say may be previous studies or pervious reports.</p>
-------------------------	--

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1 comments

I. Abstract

Under line 42 it is good if "isoniazid (INH) therapy" written as isoniazid preventive therapy(IPT) & "INH therapy" at line 51 should be replaced with IPT

(Under line 42 isoniazid (INH) therapy rewritten as isoniazid preventive therapy (IPT) & under line 52 INH therapy is replaced with IPT

II. Introduction

The abbreviation at line 5 "HIV" is well known it need to write in full word first and then use the abbreviation in the rest of the paper.

(In the first sentence at line 5 "HIV" is replaced with Human Immuno-deficiency Virus (HIV).

III. Method

The word "provinces" in line 42 is not known in Ethiopia and not clear if it mean zone or district. Therefore, it is good to replace with the word District to avoid confusion.

(The word "province" in line 42 is replaced with "district".

Page 6 in line 12,"at" need to replace by to (at hospitals replace by to hospitals)

(Page 5 in line 14 "at hospital " is replaced with "to hospital "

IV. Result

In the result line 25-27 the authors describe as follow: "The bivariate analysis showed that male patients (COR (crude odds ratio) =1.48; 95% CI: 0.99, 2.12; p-value = 0.053) were more likely to have tuberculosis compared to female patients". However, the association is not statically significant see the 95%CI (0.99-2.12) has included 1, which means the association is not statically significant.

Therefore, the association is by chance. I suggest to remove the "more likely to have tuberculosis" or the authors should rewrite as follow - Although, in bivariate analysis male patients had 1.48 times more likely to have TB compared to female patients, the association is not statically significant.

(Page 8 in line 27; the association of TB and gender is rewritten as. Although, in bivariate analysis male patients had 1.48 times more likely to have TB compared to female patients, the association is not statically significant.

V. Discussion

Page 13 Line 29-3: When compared with female HIV positive adults, we found that male HIV positive adults were more likely to develop TB. Men are reported to be more susceptible to tuberculosis infection. I think the association between male sex and TB infection among male patients who have HIV infection is not statically significant even in the bivariate analysis. The association is mainly due to chance (95%CI) include 1 which showed t no statically difference between male and female. The Authors may discuss in the other way round which means indicating no association between HIV/TB infection and sex difference and discuss what it mean comparing with other similar studies.

Otherwise, good to remove this sentences.

(The following sentence has been removed. "When compared with female HIV positive adults, we found that male HIV positive adults were more likely to develop TB. Men are reported to be more susceptible to tuberculosis infection."

In most of discussion part the authors use "literature" elsewhere. I think it good to say may be previous studies or previous reports.

(Literature elsewhere is replaced with previous study.

Correction

Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case–control study. *BMJ Open* 2016;6:e009058. The first name of the third author was misspelt. The correct spelling is Annelies Wilder-Smith.

BMJ Open 2016;4:e009058corr1. doi:10.1136/bmjopen-2015-009058corr1



CrossMark