PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study
AUTHORS	Daba, Matiwos; Tesfaye, Markos; Adorjan, Kristina; Krahl, Wolfgang; Tesfaye, Elias; Yitayih, Yimenu; Strobl, Ralf; Grill, Eva

VERSION 1 – REVIEW

REVIEWER	Mezinew Sintayehu Debre Markos University, Ethiopia
REVIEW RETURNED	27-Dec-2020

GENERAL COMMENTS	regarding the methods 1. There are traditional alcohols which are most commonly consumed. how do you standardize those units? it is not clear and is difficult to measure the unit. even many of alcohols have not a specified percentage of alcohol content. so, the instrument is not clear and doesn't seem plausible. 2. is there the so-called khat use disorder? where did you get? can the scientific world understand you? try to use the appropriate word. regarding ethics what has been done for those who have a problem of alcohol and khat use? it is not mentioned. ethically responsible regarding references some of the references don't go in line with the text cited. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Asmare Belete Department of Psychiatry, College of Medicine and Health Science, Wollo University Dessie, Ethiopia
REVIEW RETURNED	29-Dec-2020

GENERAL COMMENTS	Comments to the Author Thank you for the opportunity to review the manuscript entitled, “Khat and alcohol use disorders predict poorer adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study. The manuscript is crucial because it add awareness and evidence based data that the influence of khat and alcohol use disorder on medication adherence. The potential of the research in contributing to the literature the manuscript needs some minor revisions before it is ready for publication consideration. The issues that need to be addressed are spelt out below:

	Limitation of the study: you put the strength of the study; in addition you expected to add limitation of your study on separate part on your manuscript? Referenced: you incorporated reference which is out dated like reference no 9. Please amend with up-to-dated reference. General Comments 1) The manuscript still needs thorough English language editing. 2) I can recommend a publication of this manuscript.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers

1. in most of your document you describe by saying substance use disorder which is not consistent with your title.

Response: We have defined what substance use disorder is in this study on page seven. We understand that substance encompasses a wide range of psychoactive chemicals. However, in this study substance use disorder is limited to khat and alcohol use disorder since we did not find other substance use disorders in the study population. We also amended the title as **Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study.**

2. why you make your title sentence? it doesn't seem title of a research that shows the purpose of the study.
   Response: We are grateful for your comment on the title. We amended the title of the manuscript as **Substance use disorders and adherence to anti-tuberculosis medications in Southwest Ethiopia: A prospective cohort study.**
3. do you think food insecurity, and sub-saharan africa are key words? they are not
   Response: Thank you, we have now removed food insecurity and sub-Saharan Africa from the keywords.
4. this information doesn't seem realistic. imagine, it says it is bigger than the general population. even the references you cite don't go inline with the text here.
   Response: Thank you for the comment. We tried to mention as substance use is prevalent among TB patients, for example, in reference number 19 (O'Connell R etal), it was reported that" The highest prevalence of alcohol dependence was observed among HIV-test unknown **TB patients** (34.7%), and lowest was among HIV positive patients on treatment but **without TB** (14.1%)". The sentence in the paragraph is amended as follows: Substances such as alcohol, tobacco, khat, and illicit drugs are commonly used among patients with TB. Also, we replaced the other two references.
5. is there the so called khat use disorder? where did you get?
   Response: we operationalized khat use disorder on page 9 line 30-33. In this study, khat use disorder was defined as frequent khat use and using more than one bundle of khat per day. The daily consumption of khat and using more than one bundle of khat is corresponding to the DSM-5 criteria number 1, 4, and 10 for substance use. Khat falls within the broad category of amphetamines. Previous research has also reported the validity of khat use disorder as a syndrome consistent with DSM-5 criteria (Duresso et al 2016; https://pubmed.ncbi.nlm.nih.gov/27061394/).
6. There are traditional alcohols which are most commonly consumed. how do you standardize those units? it is not clear and is difficult to measure the unit. even many of alcohols have not a specified percentage of alcohol content. so, the instrument is not clear and doesn't seem plausible.

Response: In this study, patients were asked what type of spectacles to drink alcohol, and based on our previous study we standardize each unit. We cited our previous study regarding measurement and standardization of traditional alcohols (Soboka M et al), reference number 40. In the previously published data regarding local alcohol (Soboka M et al), we measured the volume of all local spectacles that people used to drink alcohol then the alcohol content of each spectacle was estimated based on the volume and ethanol content of local alcohol. The alcohol content of local alcohols in Ethiopia was estimated by a previous study in Ethiopia.

7. there is no the so called khat use disorder. where did you get this disorder/? can the scientific world understand you? try to use the appropriate word
   Response: We have operationalized khat use disorder in our study on page 9 line 30-33. In this study, khat use disorder was defined as frequent khat use and using more than one bundle of khat per day. The daily consumption of khat and using more than one bundle of khat is corresponding to the DSM-5 criteria number 1, 4, and 10 for substance use. Khat falls within the broad category of amphetamines. Previous research has also reported the validity of khat use disorder as a syndrome consistent with DSM-5 criteria (Duresso et al 2016; ttps://pubmed.ncbi.nlm.nih.gov/27061394/).
8. what is frequent here? how many times per week?...it will be good your operational if you make it very clear
   Response: The correction is made on page 8 lines 30-33 as follows. We operationalized frequent khat use in this study as using khat daily and 2-3 times per week. We acknowledge the limitations of not using the entire DSM criteria for diagnosis but our goal was to achieve adequate sensitivity because denial of substance use related behaviour is common.
9. what has been done for those who have a problem of alcohol and khat use?
   Response: We amended the manuscript on page 11 line 29-31 as follows: The study participants who had alcohol and khat use disorder were advised to contact a mental health professional for further evaluation and treatment.
10. i think you can't say 50%. how you withdraw and arrive at 50%. it may not be.
    Response: As this study is a prospective cohort study, we recruited 50% of patients with substance use disorder (alcohol and khat use disorder) and 50% who were free from substance use disorder. So, we intentionally recruited an equal number of patients with substance use disorder and without substance use disorder. This means out of 268 participants, 134 of them were in the group with substance use disorder and 134 were in the control group (free of substance use).
11. why you classified in to two? is this the write way?
    Response: We categorize education in two categories because there was a small number of participants in one cell which is difficult to further categorize it more than the current one.
12. could those reasons be the reason for non adherence for the variable of ' over time' or time? or are you listing the general factors of non adherence?
    Response: Yes, here we listed factors that were previously known to affect adherence over the course of treatment. These factors were assessed in many studies in the past but substance use disorder was not.
13. is this necessary information? do you think these could be mentioned as strength?
    Response: Thank you, the prospective design of the study adds to the quality of data compared to retrospective designs. In addition, as establishing temporal relationship is one criteria for establishing causality, we mentioned it as one advantage over cross-sectional assessment of our exposure and outcome variables. Also, reporting about strengths and limitations are important as it shows what was done what needs improvement in the future. Furthermore, reporting strengths and limitations are among the requirements of the journal.
14. imitation of the study: you put the strength of the study; in addition you expected to add limitation of your study on separate part on your manuscript?
    Response: Limitations and strength of the study were reported separately on page 21 ad 22.

However, on the 3rd page of the manuscript, both are combined because it is the format required by the journal.

15. referenced: you incorporated reference which is out dated like reference no 9. Please amend with up-to-dated reference.
    Response: we accepted the comment and replaced the reference with up to date one.

VERSION 2 – REVIEW

REVIEWER	Mezinew Sintayehu Debre Markos University, Ethiopia
REVIEW RETURNED	22-Feb-2021

GENERAL COMMENTS	Objective: the objective is not specific and focused since the exposure is not clear. Was it alcohol or was it Khat or both? In a cohort study, the exposure and objective should be specific and focused. And it is not in line with the internal document. The objective and exposure are not clear and not consistent throughout the document. What is your exposure variable? Khat? or alcohol? or substance use disorder? If you say substance use disorder? What it comprises? Is it Khat and alcohol? Is it Khat or alcohol? Is it Khat and/or alcohol? These all are not clear with all the other problems I comment on in the document. Abstract: the result of association/risks is not according to the exposure it is classified in methodology. Methods: -The period of recruitment, exposure, and follow-up is not described in the study setting. . As can be seen in sample size determination, it is determined by the proportion of khat chewers and non-adherence. The research didn't consider other variables such as alcohol or others or it wasn't reasoned out. Why didn't you take/test other variables if it was said substance used disorder, why it wouldn't take another variable such as alcohol use, to get a representative sample, for taking the larger sample size after comparison? - Variable of substance use disorder is difficult to understand throughout a document including in a methods. Is it Khat and alcohol? Is it Khat or alcohol? Is it Khat and/or alcohol? -the tool of alcohol use disorder wasn't tried to standardize in this study, and the cited reference is also inadequate (40). The cited reference is not well described, and can't answer the crucial elements of measurement. It didn't include the estimated millilitres of each receptacle of traditional alcohol, and the average percentage of alcohol in each alcohol beverages is also not mentioned. Therefore we can conclude that the measurement is not right and/or not explained well. According to the above mentioned, the author can say alcohol use rather than alcohol use disorder. -regarding the exposure variable of Khat use disorder, normally, Substance use disorder/stimulant use disorder is a scientific diagnostic term developed by DSM_5, and it has its criteria. It can't be said or use this diagnostic term by the operational definition the authors write in a document. They may say problematic Khat use or other common terms with reference, but they can't say khat use disorder. The criteria they set and a variable they named is different, and can't go together.

	-Was the data collectors blind on the exposure status of the participant? Result: lost to follow up was not available. Is it plausible? -Regarding measure of the event frequency of outcome, Prevalence or incidence especially for first and second follow up? Why don't they use incidence? -Why they used RR rather than OR? and why they considered Absolute risk? Relative risk is the appropriate measurement of association in the cohort study. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer

1. Objective: the objective is not specific and focused since the exposure is not clear.

Response: Thank you for this remark. The objective of this study is now clear and it is stated in lines 9-12 of the abstract and on page 6 lines 3-8. The exposure variable in this study is substance use disorder; this is stated on page 7 lines 33-56 and page 8 lines 1-35. The information about objectives and exposure is now focused and clear.

2. Was it alcohol or was it Khat or both? In a cohort study, the exposure and objective should be specific and focused. And it is not in line with the internal document. The objective and exposure are not clear and not consistent throughout the document.

Response: The objective of this study is to assess the effect of substance use disorders on adherence to anti-TB medications. We have already operationalized substance use disorders in this manuscript on page 7, lines 36-41. Throughout the document, the exposure and objective are now clearly reported.

3. What is your exposure variable?

Khat? or alcohol? or substance use disorder?

Is it Khat or alcohol?

Is it Khat and/or alcohol?

These all are not clear with all the other problems I comment on in the document.

Response: Our exposure variable was substance use disorder. That means that patients with alcohol and/or khat use disorders were considered as exposed while patients without any substance use disorders were considered as unexposed participants of the study. Substance use disorder which includes alcohol and khat is our exposure variable and this is operationalized on page 7 lines 36-42. To make it more clear, we added the following about exposure variable on page 7 lines 34-36: "In this study, the exposure variable is substance use disorder which includes khat and/or alcohol use disorder."

4. Abstract: the result of association/risks is not according to the exposure it is classified in methodology.

Response: Here we edited as follows: Patients with khat use disorder were 3.8 times more likely to be non-adherent to anti-TB medications than patients without khat use disorder (aOR 3.8, 95%CI=1.8-8.0).

5. Methods: -The period of recruitment, exposure, and follow-up is not described in the study setting.

Your objective is not specific and focused, Especially since your exposure is not clear. Was it alcohol or was it Khat or both? In a cohort study, the exposure and objective should be specific and focused. And it is not in line with the internal document.

Response: In the introduction, we amended the objective of the study on the next page (page 5, lines 1-6) as follows: “Therefore, the objective of this study is to assess the effect of substance use disorders (including alcohol and khat) on adherence to anti-TB medications in Southwest Ethiopia.”

6. period of recruitment, exposure, follow up is not described.

Response:

We have specified the data collection time which also includes recruitment of patients. So, on page 6 lines 43-46 we mentioned the period of patients recruitment and data collection. Patients were recruited during the first six months. All patients were followed for six months (i.e from the beginning until the completion of DOTS). On the same page (page 6) lines 51-58 and on page 7 lines 36 to 56, page 8 lines 1-35 we have mentioned the follow-ups. The exposure is mentioned on page 7 under the topic exposure variable.

7. was this matched or unmatched? mention it

Response: In this study, we did not pair exposed and non-exposed patients by a certain character.

8. As can be seen in sample size determination, it is determined by the proportion of khat chewers and non-adherence. The research didn't consider other variables such as alcohol or others or it wasn't reasoned out. Why didn't you take/test other variables if it was said substance used disorder, why it wouldn't take another variable such as alcohol use, to get a representative sample, for taking the larger sample size after comparison?

Response: We did not ignore other substance use disorders but we could not find published data regarding alcohol or other substance use and adherence among patients with TB. The only data we got at that time was the proportion of adherence among patients who use khat. For this reason, we took the proportion of non-adherence among TB patients who use khat.

9. "the summation of having disorder related to alcohol and khat" this phrase is not clear.

Response: We edited it as follows: In this study substance use disorder was defined as having khat and/or alcohol use disorder.

10. the tool of alcohol use disorder wasn't tried to standardize in this study, and the cited reference is also inadequate (40). The cited reference is not well described, and can't answer the crucial elements of measurement. It didn't include the estimated millilitres of each receptacle of traditional alcohol, and the average percentage of alcohol in each alcohol beverages is also not mentioned. Therefore we can conclude that the measurement is not right and/or not explained well. According to the above mentioned, the author can say alcohol use rather than alcohol use disorder.

Response: The tool we have used to assess alcohol use disorders is developed by WHO and standardized in many developed and developing countries. So, there is no reason to say alcohol use instead of alcohol use disorder, while we are using AUDIT. In this study, we cited a previous study that reported local alcohols in Ethiopia using the same tools. So, we have added these reference for further clarification. The previous study did not add the volume and milliliters of alcohol. We already

have the volume of each receptacle and alcohol content. Since our aim is not to report about volume and alcohol content of local drinks we did not include this information in the current and previous studies. However, the information regarding the volume of local receptacles is available for upon request. In general, AUDIT was used in many studies in Ethiopia. So, since we have used a validated tool we are expected to report the findings according to the tool. Therefore, we are interested to keep the term alcohol use disorder in our study.

11. Substance use disorder is a scientific diagnostic term developed by DSM_5, and it has its criteria. You can't say or use this diagnostic term by the operational definition you set above. You may say problematic chat use or others with reference, but you can't say khat use disorder. The criteria you set and a variable you name is different, and can't go together.

Response: We are not saying we have used diagnostic criteria but our questions to assess khat use disorder were corresponding to DSM-5 Criteria. Using the term khat use disorder is acceptable as it will open the door for future research in this area. While we are using a screening tool, we can use diagnostic terms in the Diagnostic and Statistical Manual of Mental Disorders, for example, we use the term alcohol use disorder based on the screening tool, AUDIT, or others. We use the term tobacco dependence (tobacco use disorder) using a screening tool, The Fagerström Test for Nicotine Dependence. It is clear that the screening tools are not golden standards and have limitations to diagnose substance use disorder but still we would like to keep these terms and we discussed the limitations of our operational definitions as we interpreted the findings.

12. Was the data collectors blind on the exposure status of the participant?

Response: They were not blind to the exposure. During data collection, the patients were reporting about their substance use to data collectors.

13. Here it states that the patient having both Khat and alcohol use disorder means having both disorders as co-morbid at once, which creates another unclear and unfocused exposure on top of the ambiguous operational definition of substance used disorder. The objective and exposure are not clear and not consistent throughout the document.

What is your exposure variable?

Khat? or alcohol? or substance use disorder?

If you say substance use disorder? What it comprises?

Is it Khat and alcohol?

Is it Khat or alcohol?

Is it Khat and/or alcohol?

These all are not clear with all the other problems I comment on in the document.

Response: The exposure variable is substance use disorder and we have mentioned this on page 7. Also on the same page, 7 lines 36-42 substance use disorder is operationalized as having khat and/or alcohol disorder. From this definition, we have now clarified that substance use disorder in this study includes khat and/or alcohol use disorder. The definition here is not about comorbidity.

14. Lost to follow up was not available. Is it plausible?

Response: In our study, we have no loss to follow up. This is unusual but perhaps the nature of DOTS regimen for TB played a role. Because in Ethiopia there is a strict follow-up of TB patients who are on DOTS and patients who miss appointments are traced by their home address so that they continue their treatment. Health extension workers work in collaboration with health centers and hospitals in tracing patients who missed appointments by going to the patients' homes frequently.

15. Regarding measure of the event frequency of outcome, Prevalence or incidence especially for first and second follow up? Why don't they use incidence?

Response: We were interested to report prevalence rather than focusing on the rate of patient who developed non-adherence to anti-TB medications during the follow-up. Because prevalence measures the proportion of patients who have non-adherence at and during the follow-ups. But the incidence only measures the rate of patients who only became non adherent at a specific follow-up time point. Prevalence allows us to categorize individuals who have been non-adherent in the past and continue to be non-adherent at the subsequent follow-ups.

16. Why they used RR rather than OR? and why they considered Absolute risk? Relative risk is the appropriate measurement of association in the cohort study.

Response: We used OR and aOR not RR or absolute risk. We used odd ration to measure the association between the exposure (substance use disorder) and outcome (adherence).

VERSION 3 – REVIEW

REVIEWER	Mezinew Sintayehu Debre Markos University, Ethiopia
REVIEW RETURNED	05-May-2021

GENERAL COMMENTS	More than 2/3 rd of the previous comments and questions are not answered. with those unclear and non-evidenced measurements of substance variables (alcohol, Khat), you can't say substance use disorder. You may say substance use or any other terms used in psychoactive substance. To use the term substance use disorder, we have to use a standardized epidemiological tool or requires professional diagnosis. The period of recruitment, exposure, follow-up is not described. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 3 – AUTHOR RESPONSE

Responses

1. with those unclear and non-evidenced measurements of substance variables (alcohol, Khat), you can't say substance use disorder. You may say substance use or any other terms used in psychoactive substance. To use the term substance use disorder, we have to use a standardized epidemiological tool or requires professional diagnosis. The period of recruitment, exposure, follow-up is not described.

Response: We have already reported that we used AUDIT which was developed by WHO to assess alcohol use disorder but there is no tool to assess khat use and use disorder. So, we used questions which are in line with the Diagnostic and Statistical Manual of Mental Disorders as reported it in previous comments. So, we are interested to keep the term 'substance use disorder' because we have used standardized epidemiological tool for alcohol use disorder and questions which can pick

khat used disorder. Also, in the limitation part we have reported that the tool we have used were not diagnostic tool even though they are standard tool.

Regarding recruitment, exposure, follow-up, we have already mentioned them in the manuscript on page 6 and 7.

2. where is a variable (both Khat and alcohol use), that means poly subsatnce. you only mentioned khat use and alcohol use independently

Response: We acknowledge the reviewer comment. But we were interested to look at the effect of each substance on adherence to anti-TB separately. Also, we have already operationalized that 'substance use disorder' in this study is equivalent to khat and alcohol use disorder. That is why we are using both terms interchangeably. That means when are talking about substance use disorder in this study we are also talking about khat and alcohol use disorder.

3. with those unclear and non-evidenced measurements of substance variables (alcohol, Khat), you can't say substance use disorder. You may say substance use or any other terms used in psychoactive substance. To use the term substance use disorder, we have to use a standardized epidemiological tool or requires professional diagnosis. The period of recruitment, exposure, follow-up is not described.

Response: This part is repetition of comment number one. So, we have already reacted to the comment. Here is additional explanation: We have used standard tool to assess alcohol use disorder but there is no tool to assess khat use or khat use disorder. So, we are in line with your comment. All standard tools used to assess substance use disorder are not golden standard for the diagnosis of substance use disorder but they are screening tool. So, in this study using the term is substance use disorder is right. We can use the term 'Substance use disorder' in this study because we used AUDIT which is standard tool to asses alcohol use disorder and developed questions in line with standard tool to assess khat use disorder.

4. period of recruitment, exposure, follow up is not described.

Response: The participant recruitment is mentioned on page 6 line 43 and page 7 lines 20-26. Also, the exposure is described well on page 7 lines 31-55 and page 8 lines 1-41. Also follow up is already mentioned on page 6 lines 51-57. We have mentioned this in the previous comment but we are not clear why the reviewer ask similar question while there is clear information in the document.

5. was this matched or unmatched? mention it

Response: In this study, we did not pair exposed and non-exposed patients by a certain character. We included this information in the document.

6. As we can see here in sample size determination, it is determined by khat chewers and non-adherence. You didn't consider other variables such as alcohol or others. Why didn't you take/test other variables if you said substance used disorder, to get a representative sample, for taking the larger sample size?
   Response: We have already mentioned this in the previous response as follows: We did not ignore other substance use disorders but we could not find published data regarding alcohol or other substance use and adherence among patients with TB. The only data we got at that time was the proportion of adherence among patients who use khat. That is why we took the proportion of non-adherence among Tb patients who use khat. Also, the proportion is we used was close to 50% which can give good sample size. We appreciate the reviewer concern, and we think that this clarification is adequate and can address the concern of reviewer.

7. You didn't try to standardize the alcohol toll in this study, and the reference you cite is also inadequate (40). The article you cite is not well described, and can't answer the crucial elements of measurement. The author didn't write the estimated millilitres of each receptacle for traditional alcohol usage, and the average percentage of alcohol in each alcohol beverages is also not mentioned. Therefore we can conclude that your measurement is right and/or not explained well. According to the above mentioned, you can say alcohol use rather than alcohol use disorder.
   Response: We appreciate the reviewer comment but we cited the only study that mentioned about AUDIT and standardization of traditional alcohol use in Ethiopia. The main issue here is how can we say alcohol use while using standard tool which is adapted to local culture to assess alcohol use disorder? So, we are interested to keep alcohol use disorder.
8. Substance use disorder is a scientific diagnostic term developed by DSM_5, and it has its criteria. You can't say or can't use this diagnostic term by the operational definition you set above. You may say problematic chat use or others with reference, but you can't say khat use disorder. The criteria you set and a variable you name is different, and can't go together.

Response: We are grateful for reviewer comment. When there is no tool to assess khat use and use disorder the only option is developing questions based on literature reviews and DSM-5 criteria. So, the questions to assess khat use disorder were developed considering the above important information. So, the daily consumption of khat and using more than one bundle of khat is corresponding to the DSM-5 criteria number 1, 4, and 10 for substance use. Khat falls within the broad category of amphetamines. Previous research has also reported the validity of khat use disorder as a syndrome consistent with DSM-5 criteria (Duresso et al 2016; https://pubmed.ncbi.nlm.nih.gov/27061394/). Therefore, we interested to keep this term khat use disorder because it also supported by literature. Also, this term is import as it invite researchers to conduct more study on khat which will be helpful to include this substance in the future DSM criteria. Last, while using screening question, we can use the term 'substance use disorder' but that does not mean that the tool is golden standard to diagnosis substance use disorder. Similarly, while using questions in line with DSM-5 criteria, we can say khat use disorder but that does not mean these questions can diagnose khat use disorder because they are not golden standard to diagnose khat use disorder. In general we have included some of this information in the limitation part of our study. Also, previous study clearly indicated that we can use the term "khat use disorder" and the reviewer can read for further information using this link https://pubmed.ncbi.nlm.nih.gov/27061394/

9. was the data collectors blind on exposure status of participant

Response: We have responded to this question in the past adequately and repeat it again. Data collectors were not blind to exposure status of the patient. We now included this information in the document.

10. Here it states that the patient having both Khat and alcohol use disorder means having both disorders as co-morbid at once, which creates another unclear and unfocused exposure on top of the ambiguous operational definition of substance used disorder. The objective and exposure are not clear and not consistent throughout the document.

Response: The exposure variable is substance use disorder and we have mentioned this on page 7. Also on the same page, 7 lines 42-47 substance use disorder is operationalized as having khat and alcohol disorder. From this definition, it is clear that substance use disorder in this study includes khat and alcohol use disorder. We did not add both together and say that they are comorbid. The model is clear and in line with our operational definition and objective. Also, the definition is clear and does not confuse readers.

11. Didn't you face lost to follow up? it may be not plausible

Response: We have already answered this question in the past. We are not clear why the review repeat questions which are adequately answered. There is no other answer than the previous answer which is as follows: In our study, we have no loss to follow up. Because in Ethiopia there is a strict follow-up of patients and if patients jump some appointments they will be searched by their contact address and back to treatment. Health extension workers work in collaboration with health centers and hospitals in searching patients if the patients missed appointments frequently. Lastly, it is not a must to have loss to follow up.

12. You can write and put the result about the effect of substance use, as a category, on non-adherence in this longitudinal study but not about each specific substance use you wrote in result part. Because, from the beginning your exposure are both substances and samples are determined in that way. And here again, Why don't you use RR rather than OR? And why you consider Absolute risk? Relative risk is the appropriate measurement of association in the cohort study.

Response: We have already operationalized that substance use disorder in this study represent khat and alcohol use disorder so we do not need to add substance use disorder as a separate exposure variable in addition to khat use and alcohol disorder.

We used OR and aOR not RR or Absolute risk. We used odd ration to measure the association between the exposure (substance use disorder) and outcome (adherence). It is also possible to use OR in a cohort study.

13. where is a variable (both Khat and alcohol use), that means poly subsatnce. you only mentioned khat use and alcohol use independently

Response: Since we have operationalized substance use disorder we do no need to mention it together with alcohol and khat use disorder. Also, there is no need of reporting poly substance use here. This comment is also addressed above.

14. incidence or prevalence, incidence or proportion, incidence or prevalence?

Response: We were interested to report prevalence rather than focusing on the rate of patient who developed non-adherence to anti-TB medications during the follow-up. Because prevalence measures the proportion of patients who have non-adherence at and during the follow-ups. But the incidence only measures the rate of patients who developed something (non-adherence in our case) during period of time.