## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Magnitude of optimal adherence and predictors for a low level of adherence among HIV/AIDS infected adults in south Gondar zone, Northwest Ethiopia: A multi-facility cross-sectional study |
| **AUTHORS** | Zewude, Shimeles; Ajebe, Tewodros |

## VERSION 1 – REVIEW

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| **REVIEWER** | Ibeneme, Sam<br>University of Nigeria |
| **REVIEW RETURNED** | 03-Sep-2021 |

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| **GENERAL COMMENTS** | BMJ<br>bmjopen-2021-056009<br>Review Report<br>Title: Level of adherence to antiretroviral therapy and associated factor among HIV infected<br>adults in south Gondar zone, Northwest Ethiopia<br>Reviewer: Prof. Sam Ibeneme<br>Institutional affiliations:<br>1. University of Nigeria, Enugu Campus, Department of Medical Rehabilitation, Faculty of Health Sciences, Enugu, Nigeria. sam.ibeneme@unn.edu.ng.<br>2. Department of Physiotherapy, Faculty of Health Sciences, School of Therapeutic Studies, University of the Witwatersrand, 7 York Road, Parktown, 2193 Johannesburg, South Africa<br>Reviewers Report<br>General comments<br>Many thanks for inviting me to review the suitability of the article Level of adherence to antiretroviral therapy and associated factor among HIV infected adults in south Gondar zone,<br>Northwest Ethiopia' for publication. Essentially, this article sought to (1) "identify levels of adherence to ART drugs and (2) identify factors associated with them (levels of adherence to ART drugs) in northwest Ethiopia. It further hypothesized that in the era of COVID-19 adherence level to ART among people living with HIV have been jeopardized". Invariably, it sought to explore the explanatory variables for the variance in levels of adherence to ART drugs among HIV infected adults in the south Gondar zone, Northwest Ethiopia, using predictive models. Therefore, they studied 432 adults living with HIV that received ART for at least three months before the study. They utilised a cross-sectional study design and employed a systematic sampling technique in recruiting the participants. The study measured adherence using two self-reported instruments whose validity and reliability was not provided. The cut-off for a different level of adherence was not provided. The study found an 81.5% adherence level among the participants which was interpreted as a low level of adherence. |

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| | The study also identified Stigma or discrimination, missed scheduled clinical visits, being on anti-TB treatment, recent CD4 cells cunt less than 500 cell/mm3 and patients in WHO clinical stage three at the time of ART initiation as predictors of the level of adherence. Overall, these findings suggest that socio-cultural beliefs/practices (which mainly underlie discrimination,), health-seeking behaviour (which underlie missed scheduled clinical visit), co-morbidity of TB and disease severity (which is measured by the WHO staging of HIV and CD4 count <500cells/mm3) may have a role in determining the level of medication adherence. These predictors should be prioritised in the clinical management and policy interventions to address drug resistance variants of the HIV disease which can be mitigated by optimal adherence to ART medication considering the impact of adherence virologic failure. Thus, I consider this study to be original, useful, timely and relevant.<br>Specific Comments<br>Following a preliminary review of this article, I find this paper quite interesting and an important scientific contribution towards understanding how the level of adherence to ART vary in PLWHA and identifying the explanatory variables that account for these differences. However, there are specific issues that need to be addressed to improve the quality of this paper.<br><br>Abstract<br>Background: The objectives of the study were clearly stated.<br>Method: The research design is not so clear. Does one wonder whether this was a descriptive cross-sectional study or an observational cross-sectional study or a descriptive observational study? It must be indicated whether the p-value was one-tailed or two-tailed to give proper context when interpreting it. The explanatory variables that were explored in the regression analysis must be mentioned.<br>Primary and secondary outcome measures: The authors indicated that the primary outcomes were “magnitude of optimal adherence and predictors for a low level of adherence were assessed.”: The authors need to rewrite this area because it seemed that they already knew that there was a low level of adherence to ART before the study. if that was the case, why the study? However, it is best to state the primary outcomes as:<br>i. levels of adherence to ART drugs and<br>ii. Please mention the specific predictors for a level of adherence that was considered in the study.<br>Conclusion: the authors did not mention the implication of the relationships in the conclusion. For instance, CD4+ count enables the assessment of HIV symptom severity which should have an impact on emotional wellbeing and decision to continue adhering to medications when such symptoms become more severe. Similarly, discrimination alludes to socio-cultural factors which influence people's lifestyle, beliefs about an illness and way of life. Therefore, the implications of these findings should be given the proper context to appreciate the importance of these factors in medication adherence behaviour or health-seeking behaviour.<br>Main study<br>Background:<br>1. The background to this study was well written and provides a good rationale for the present study.<br>2. Lines 94 & 95 are unclear and should be written in clear language. |

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| | 3. I observe that a hypothesis was stated in the abstract but not in the Introduction area of the main study. in any case, the study hypothesized that “in the era of COVID-19 adherence level to ART among people living with HIV have been jeopardized.” Nowhere in this paper was the word "jeopardised" operationalised. It is difficult to relate it to any specific cut-off to enable us to have an estimate of the point at which adherence is jeopardised. Perhaps, the authors may think of stating it differently. For instance, it is hypothesised that "in the era of COVID-19 adherence level to ART among people living with HIV have been sub-optimal or less than 90%.” This is a directional hypothesis and requires that only a one-tailed p-value should be determined. This information was not provided in the abstract or the main study.<br><br>Method:<br>4. The research design suggests that this is a descriptive cross-sectional study. It must be clearly stated so that there is a distinction bearing in mind that there are other types of cross-sectional study which fulfil other research purposes. Also, since this study was done among people with HIV and not AIDS, the defining cut-off point for the CD4+ cell count must be stated in the inclusion criteria.<br>5. It was not indicated whether the patients were in-patients or out-patients. This is important because if they were in-patients, then pharmacy records would have been the appropriate tool for measuring ART adherence.<br>6. The test instruments were two. However, it was not indicated what each of them measured. The various sections of the instrument were not described to give an insight into the measurement items or what outcomes were measured.<br>7. It was not indicated what the predictors of ART adherence were and how they were identified.<br>8. The primary and secondary outcomes were not identified in the main study but some were mentioned under the abstract.<br>9. Lines 137 & 138 were unclear. I do not understand what the words “retrieves” and “incorrect” meant in those sentences. The sentences read out of context.<br>10. Please rewrite line 151. It states that “Data entry and editing were performed by EPI info and then exported to SPSS version 23”. Consider replacing the words - “by EPI” with “using EPI”.<br>Measures and data collection<br>In lines 147 – 148, page 7, it was stated that a pilot study was conducted but the result of the pilot was not indicated as regards the validity and reliability of the test instrument. The validity and reliability of the test instruments must be indicated especially since it has been adapted and translated into Amharic.<br>Data Analysis<br>It is important to indicate whether the p was one-tailed or two-tailed. This is important because this study is driven by a directional hypothesis in which case a one-tailed p-value should be appropriate.<br>Results<br>1. The result section was well written.<br>2. Lines 171 and 172 should be rewritten to make it clear what the authors intended to communicate.<br>Discussion<br>1. Line 222 should be written in correct English.<br>2. I think that the authors need to be clear that the fallout of sub-optimal adherence to ART medication could lead to the emergence of the resistance variants of HIV. This is distinct from |

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| | non-retention in care or treatment which deals with loss to follow-up. Sometimes the authors mixed up both. Since the authors recruited participants who were still retained in care at the various hospitals, the context for discussing the findings should be whether there was sub-optimal adherence, but not retention in care.<br>3. From the results, the most important predictor of adherence level is WHO clinical stage three, followed by CD4 count <500 cells/mm3. Both of these are measures of disease severity. Therefore, the health belief models should have been used to explore the adherence behaviour to give deeper insight on the key drivers of ART adherence behaviour or health-seeking behaviour in this population.<br>4. The authors in the introduction (see page 2, line 95), "hypothesized that HIV burden may be an important predictor for the physical and mental health of this population." However, it is not discussed whether this hypothesis was realised, and should be reflected in the discussion.<br>Conclusion<br>I do not agree with the conclusion on lines 250 & 251, page 12, which states that "This study demonstrated that level of adherence was relatively low compared with other local studies." Because a study was done in Ethiopia (Addis Ababa city) cited by the authors reported an adherence level of 73% (see the reference list, No. 15). Please I suggest the authors rewrite this sentence as follows: "This study demonstrated that level of adherence was relatively low compared with some local studies."<br>Strength & limitation<br>i. The cross-sectional design used in this study cannot be used to analyze behaviour over a period exceeding 2-4 weeks.<br>ii. Does not help determine cause and effect.<br>iii. The timing of the snapshot is not guaranteed to be representative.<br>iv. Cross-sectional data consist of observations of many subjects at the same point in time. The time interval between tests or administrations in a cross-sectional study is, typically, two to four weeks. Malhotra, N. K. (2010, p. 287). However, this study lasted from August 2020 to January 2021. This suggests a longer time-lapse than a snapshot would require.<br>Orthographic check<br>There is a need for a minor orthographic check of the manuscript.<br>Other Comments<br>This is a novel study that provided scientific findings that may have useful application in the clinical management and policy interventions of HIV disease. However, the procedure and approach for the study could be organised more systematically. For instance, a stepwise approach should have been adopted when reporting the procedure for the study: The stepwise procedure could involve the following steps: -<br>i. 1. eliciting a list of all potential determinants via literature review,<br>ii. 2. interviewing patients, and consulting an expert panel to identify potential determinants of medication adherence behaviour in the target population.<br>iii. 3. This is followed by embedding the determinants in a theoretical framework to provide insight on their predictive weights and points of influence on their decision to adhere to medication, and<br>iv. 4. developing a questionnaire, or choosing adherence measurement methods. |

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| | Missing sections<br>The following sections are missing at the back end of this manuscript and should be provided by the authors in line with the journal format and style, including:<br>- who must be contacted for access to the data. |

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| **REVIEWER** | GebreEyesus, Fissha |
| **REVIEW RETURNED** | 04-Sep-2021 |

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| **GENERAL COMMENTS** | Most of my comments and concerns are mentioned in separate Ms word. In the introduction section most of your reference was outdated and your discussion was shallow too. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Reviewer Comments
Thank you very much for your constructive and fruitful comment. I got many lessons from your comment and motivated me to have further references. Please find below the listed response based on your requested comment.
Abstract section
Method: The research design is not so clear. Does one wonder whether this was a descriptive cross-sectional study or an observational cross-sectional study or a descriptive observational study? It must be indicated whether the p-value was one-tailed or two-tailed to give proper context when interpreting it. The explanatory variables that were explored in the regression analysis must be mentioned.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and we clearly describe the types of a cross-sectional study and stated the types of the p-value( in method section) including explanatory variables that were explored in the regression analysis.
Primary and secondary outcome measures: The authors indicated that the primary outcomes were “magnitude of optimal adherence and predictors for a low level of adherence were assessed.”: The authors need to rewrite this area because it seemed that they already knew that there was a low level of adherence to ART before the study. if that was the case, why the study? However, it is best to state the primary outcomes as:
i. levels of adherence to ART drugs and
ii. Please mention the specific predictors for a level of adherence that was considered in the study.
Response: Thank you! The comments were taken and the manuscript was reviewed in detail and important modification was made in primary and secondary outcome measures.
Conclusion: the authors did not mention the implication of the relationships in the conclusion. For instance, CD4+ count enables the assessment of HIV symptom severity which should have an impact on emotional wellbeing and decision to continue adhering to medications when such symptoms become more severe. Similarly, discrimination alludes to socio-cultural factors which influence people's lifestyle, beliefs about an illness, and way of life. Therefore, the implications of these findings should be given the proper context to appreciate the importance of these factors in medication adherence behavior or health-seeking behavior.
Response: Thank you! The comment is well taken and the conclusion was written again with proper interpretation and consistent course of action need was stated.
Main study
Background section
Lines 94 & 95 are unclear and should be written in clear language.

Response: Thank you! The comment is well taken and this part is re-written again in clear language.
I observe that a hypothesis was stated in the abstract but not in the Introduction area of the main study. In any case, the study hypothesized that “in the era of COVID-19 adherence level to ART among people living with HIV have been jeopardized.” Nowhere in this paper was the word "jeopardized" operationalised. It is difficult to relate it to any specific cut-off to enable us to have an estimate of the point at which adherence is jeopardised. Perhaps, the authors may think of stating it differently. For instance, it is hypothesised that "in the era of COVID-19 adherence level to ART among people living with HIV have been sub-optimal or less than 90%.” This is a directional hypothesis and requires that only a one-tailed p-value should be determined. This information was not provided in the abstract or the main study.
Response: Thank you! the comment is well taken and we went to mean that, Currently our world including Ethiopia has been struggling to prevent and control a new pandemic disease called SARS-COV-2 however, chronic diseases like HIV/AIDS were put aside especially in developing countries. We hypothesize that there would be suboptimal adherence to ART drugs among people living with HIV so a one-tailed p-value was applied.
Method section
The research design suggests that this is a descriptive cross-sectional study. It must be clearly stated so that there is a distinction bearing in mind that there are other types of cross-sectional study which fulfil other research purposes. Also, since this study was done among people with HIV and not AIDS, the defining cut-off point for the CD4+ cell count must be stated in the inclusion criteria.
Response: Thank you! The comment is well taken and the study includes individuals infected by HIV/AIDS, necessary modification was made in the manuscript.
It was not indicated whether the patients were in-patients or out-patients. This is important because if they were in-patients, then pharmacy records would have been the appropriate tool for measuring ART adherence.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and the study participants were adult people living with HIV/AIDS (≥18 years old) treated as out-patients in selected public hospitals and who have been on treatment for more than three months.
The test instruments were two. However, it was not indicated what each of them measured. The various sections of the instrument were not described to give an insight into the measurement items or what outcomes were measured
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and the various section of the instrument was described.
It was not indicated what the predictors of ART adherence were and how they were identified.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and predictors of ART adherence were clearly stated.
The primary and secondary outcomes were not identified in the main study but some were mentioned under the abstract.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and primary and secondary outcomes were identified in the main study @ line number 204 to 205.
Lines 137 & 138 were unclear. I do not understand what the words “retrieves” and “incorrect” meant in those sentences. The sentences read out of context.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and it was written again.
Please rewrite line 151. It states that “Data entry and editing were performed by EPI info and then exported to SPSS version 23”. Consider replacing the words - “by EPI” with “using EPI”.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and it was written again.
In lines 147 – 148, page 7, it was stated that a pilot study was conducted but the result of the pilot was not indicated as regards the validity and reliability of the test instrument. The validity and reliability of the test instruments must be indicated especially since it has been adapted and translated into Amharic.

Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and the result of the pilot study was described with validity and reliability of the instrument.
It is important to indicate whether the p was one-tailed or two-tailed. This is important because this study is driven by a directional hypothesis in which case a one-tailed p-value should be appropriate.
Response: Thank you! The comment is well taken. We hypothesize that there would be suboptimal adherence to ART drugs among people living with HIV so a one-tailed p-value was applied.
Results section
Lines 171 and 172 should be rewritten to make it clear what the authors intended to communicate.
Response: Thank you! The comment is well taken and it was rewritten again with clear language.

Discussion section
I think that the authors need to be clear that the fallout of sub-optimal adherence to ART medication could lead to the emergence of the resistance variants of HIV. This is distinct from non-retention in care or treatment which deals with loss to follow-up. Sometimes the authors mixed up both. Since the authors recruited participants who were still retained in care at the various hospitals, the context for discussing the findings should be whether there was sub-optimal adherence, but not retention in care.
Response: Thank you! The comment is well taken and as you stated the study was conducted on individuals on follow-up and whether there is optimal adherence or not. So we take precautions to avoid collision of lost to follow up and sub-optimal adherence.
Conclusion section
I do not agree with the conclusion on lines 250 & 251, page 12, which states that “This study demonstrated that level of adherence was relatively low compared with other local studies." Because a study was done in Ethiopia (Addis Ababa city) cited by the authors reported an adherence level of 73% (see the reference list, No. 15). Please I suggest the authors rewrite this sentence as follows: “This study demonstrated that level of adherence was relatively low compared with some local studies.”
Response: Thank you! The comment is well taken and the correction was made in this section
Strength & limitation
Cross-sectional data consist of observations of many subjects at the same point in time. The time interval between tests or administrations in a cross-sectional study is, typically, two to four weeks. Malhotra, N. K. (2010, p. 287). However, this study lasted from August 2020 to January 2021. This suggests a longer time-lapse than a snapshot would require.
Response: Thank you! The comment is well taken. We collect socio-demographic, clinical, adherence level, and immunological records from patients treated by out-patients service at one time during their clinic visit. It does not mean that we were following them for six month

Orthographic check
There is a need for a minor orthographic check of the manuscript.
Response: thank you! The comments were taken; task requesting experts were rigorously considered and professionals are involved in revising the manuscript.
Other Comments
This is a novel study that provided scientific findings that may have useful application in the clinical management and policy interventions of HIV disease. However, the procedure and approach for the study could be organised more systematically. For instance, a stepwise approach should have been adopted when reporting the procedure for the study.
Response: Thank you! The comments were taken. The study were well organized systematically and scientifically.
Missing sections

The following sections are missing at the back end of this manuscript and should be provided by the authors in line with the journal format and style, including: who must be contacted for access to the data.
Response: possible to contact corresponding authors to access the data with a reasonable request.
Reviewer # 2
I went to thank you for your constructive comment and important question. Please see it below the response for the requested revision.
Title
Title should tell readers when the study was conducted? In this paper the title didn't answer when the research was carried out.
Response: Thank you! The comments were taken. We stipulating when the study was conducted in the method section.
Introduction section
Please update HIV statistics with recent data. See UNAIDS 2020 report
Response: thank you! The comment was taken and the manuscript was reviewed in detail the HIV/AIDS statistics were updated with recent data.
A similar study was carried out in the same study setting. So, what is the purpose of conducting this study? Even out of the study area it is repetitively conducted nationwide.so, What new knowledge your study will bring for scholars? And what new solution brings for the community and for those patients who are on ART?
Response: thank you! The comment was taken. Adherence is a biological and social process that changes with time. Periodic determination of ART drug adherence provides optimal HIV care, helps to develop strategy and intervention. However, the development of effective and tailored intervention requires an in-depth understanding of factors that influence it. Having a strategy to sustain an optimal level of adherence among people living with HIV is an essential step towards ensuring treatment success. again recently the world has been struggling to prevent and control a new pandemic disease called SARS-COV-2 and health institutions are given attention to this pandemic however care given to chronic diseases including HIV/AIDS put aside. This is worse especially in developing countries like Ethiopia.
There were studies conducted in this setting however many of them were determined to level of adherence to ART drugs among children so there is variation in the objective, study population, and data collection tool. Otherwise, to our knowledge, there is no recent study conducted in the study area.
Methods section
The study setting is not informative about the numbers of patients who are enrolled in ART clinic, the types of service rendered in ART clinic and the numbers of health center and hospitals which give ART service.
Response: Thank you! The comment is well taken and the manuscript was reviewed in detail and the study setting and ART service provided in the health facilities was clearly stated in the main text.
The source and study population is not described clearly rather there is duplications of study populations.
Response: Thank you! The comment is well taken and necessary modification was made in this section
The inclusion and exclusion criteria are not determined?
Response: Thank you! The comment is well taken and the comment is well taken and necessary modification was made
Why do you take margin of error (0.035)?
Response: Thank you! We have a brief and scientific response to your respected question.
- We went to estimate the prevalence level of adherence within 0.35 of an absolute level of precision. If the sample size is too small it underpowers and fails to detect the existing parameters of the study. Some authors recommended selecting a precision of 5% if the prevalence of the disease/cases is going to be between 10% and 90%, but there is no definite recommendation for the

appropriate level of precision. Investigators may also select a smaller precision than what we suggest if they wish. https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.504.2129&rep=rep1&type=pdf

- Our sample size calculation formula met the assumption of normal approximation stated by (Daniel, 1999) which says" It says that nP and n (1-P) must be greater than 5."

Why do you take the proportion of Adherence 85.3% which was carried out before 8 years? In the presence of multiple recently done studies?

Response: Thank you!

- Many study proportion of adherence was more than 90%, if we use this we end up with too small sample size.
- We have a similar study setting and again it would give us the biggest sample size, so we thought that the result would be representative when we use this population proportion (p).

why don't calculate sample size using variables?

Response: Thank you! This study had a dichotomous outcome variable so we thought a single population proportion formula was appropriate to determining sample size.

Could you explain about the validity and reliability of AIDS Clinical Trial Groups (AACTG). adherence instrument and The Community Programs for Clinical Research on AIDS (CPCRA)? Is it validated in Ethiopia?

Response: Thank you! Five AIDS experts were invited to review the Amharic version of the questionnaire for face validity and readability and it was appropriate and easy to understand by the participants. We made a pretest in order to assess its consistency. The report was further stated in the main text.

Ethical consideration should be described clearly. Did you get verbal consent or written consent?

Response: Thank you! The comment is well taken and consent was taken. Issue related to ethics was incorporated at the end of the manuscript.

Result section

Out of the total population, 257(50.2%) were in the age group between 25-34 166 years. Is it 50.2% vs 59.5% please look it again.

Response: Thank you! The comment is well taken it is to mean that 217(50.2%) and a necessary correction was made in this part.

It is better to present the result using different data presentation techniques like using figures other than tables

Response: Thank you the comment was taken

Discussion section

During discussion, first you are expected to discuss on the magnitude of adherence with similar studies conducted across different countries and put your justification for the possible difference and the second one is the variables which had statistically significant association with your outcome variable at multi variable logistic regression. in this regard your discussion is not strong and persuasive. So, you are expected to search exhaustively and waste your time on it. You are also expected to discuss on the implications of the findings in context of existing research.

Response: Thank you the comment is well taken. The discussion section is was structured with novel and recent literature and presented with strong justification and supportive evidence.

## VERSION 2 – REVIEW

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| **REVIEWER** | Ibeneme, Sam<br>University of Nigeria |
| **REVIEW RETURNED** | 02-Nov-2021 |

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| **GENERAL COMMENTS** | I recommend that the article be accepted after the authors have included a discussion on the limitations of their study. |

## VERSION 2 – AUTHOR RESPONSE

Reviewer # 1

Strength & limitation

1. The authors must include limitations to their study to guide the readers in drawing the right conclusions from the data. The cross-sectional design used in this study has limitations including the following:

i. Does not help determine cause and effect.

ii. The timing of the snapshot is not guaranteed to be representative of the true estimate of the HAART-adherence behavior in the study population.

Response: Thank you! The comment is well taken. Limitations of the study were incorporated in the discussion section of the manuscript.

2. There is a need for a minor orthographic check of the manuscript.

Response: Thank you! The comment is well taken. The Manuscript was reviewed in detail and experts were involved to structure the manuscript using conventional language.

This is a novel study that provided scientific findings that may have useful application in the clinical management and policy interventions of HIV disease

Response: Thank you!!!

Reviewer #1

Competing interests of Reviewer: I declare no competing interest in this study

Response: Thank you!!!