Author’s response to reviews

Title: Incidence and Predictors of Second-Line Antiretroviral Treatment Failure among Adults Living with HIV in Amhara Region: A multi-Centered Retrospective Follow-up Study

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Title: Incidence and Predictors of Second-Line Antiretroviral Treatment Failure among Adults Living with HIV in Amhara Region: A multi-Centered Retrospective Follow-up Study

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Dear Editor,

We thank you for the chance to resubmit our revised manuscript. Also, we would like to thank the reviewers for sharing the view and experience. The comments are very important that will
improve the manuscript. The point-by-point responses for each of the comments are provided in
the following pages. We have highlighted all changes in the revised manuscript.

We hope that the revisions meet your standards and that the paper would be published in your
journal. We look forward to working with you towards a final published product.

Sincerely,

Muluneh Alene, MPH
On behalf of co-authors

Point by point responses to queries

Reviewer-1

Comments and points raised Authors response

1. In the background section, the first two sentences of the second paragraph needs revision
to convey the correct message. The first sentence is a repetition of what is captured in the
first paragraph. ART's benefits should be highlighted but "reducing drug resistant strains"
is not an accurate description. It is better to say "Optimal adherence to ART will
minimize the development of drug resistance to ARV medication.

Answer: thank you dear reviewer for your constructive comments!

• Based on the suggestion given, we modified the statement in the revised form of the
manuscript and we make highlight for changes.

2. The information on 'response to treatment assessment' is outdated. Viral load testing is
now widely available. The authors may state that routine viral load monitoring was not
available for the period of follow-up of their study.

Answer: Thank you!

• You are right dear reviewer, during the follow-up period of the study routine viral load
monitoring was not available.
• So, as WHO recommendation (In resource limited settings where viral load monitoring is not widely available), we were assessed ART failure by clinical parameters and CD4 cell count.

• Unavailability of viral load testing which is the gold standard method for treatment failure is the limitation of the study.

• We already include it in the limitation section.

3. Describing second line treatment as the last therapeutic option is also not accurate.
Answer: thank you!

• As the suggestion given, we make revision in the revised form of manuscript.

4. The study design needs to describe the sampling technique both for the facilities where the study was conducted and the individual patients that were included in the study sample.

Was there any sample size calculation? This needs to be mentioned.

Answer: thank you again for your constructive comments!

• We agree with the comments given and we already included it in the revised manuscript.

• The sample size was determined by using sample size determination formula for survival analysis with assumptions of 95% level of confidence, and 80% power.

• But, the total numbers of patients on second line ART who fulfill the eligibility criteria in the eight selected hospitals were 1,011, and all of these were included.

1. 5. The authors mentioned that "the objective of this study was to estimate the incidence rate of treatment failure and to identify its predictors". While on "outcome and predictor variables" section, it is stated that "The outcome variable of this study was time to second-line treatment failure". The two descriptions appear to be disconnected. There needs to be consistency throughout the manuscript
Answer: thank you for your comment!

• According to the suggestion given, we already rephrased it in the revised form of the manuscript and we make highlight for changes.
6. The definition of immunologic failure that was used for the study is from the 2016 WHO definition for treatment failure. However, the timeline of the study follow-up period was from 2008-2016. The 2016 WHO definition was based on the assumption that, because of elimination of eligibility criteria to start ART, baseline CD4 count is no longer necessary to start ART and is also not being recommended for monitoring treatment. How do you reconcile this? Did the investigators make a decision of treatment failure independent of what was decided by the ART providers at the facilities. Clarify.

Answer: thank you again!

• You are right dear reviewer; the immunologic failure in this study was defined using the 2016 WHO definition for treatment failure.

• The timeline of the study follow-up period was from 2008–2016.

• The decision of treatment failure for patients on the second-line ART was given by the investigators independently using the 2016 WHO criteria.

7. On the statement, "Clients on second-line ART who were lost-to-follow-up, transferred-out, died, and remained on care without experiencing treatment failure were considered as censored", it is not clear which patients were on second line ART without 'experiencing treatment failure'. Please provide clarifying information. Answer: thank you dear!

• The follow-up period for this study was from February, 2008 and April, 2016. But, some patients didn’t achieve the treatment failure criteria in the above mentioned follow-up period (right censoring). Thus, the intension of using the phrase “remained on care without experiencing treatment failure” is just to indicate these patients.

• We included the detail clarification of this in the revised form of the manuscript.

8. On "Data collection tool and procedures", it is not clear what was used as the data collection tool. The national ART follow-up form is described as "standard data extraction checklist". The ART follow-up form is not a checklist; it is a patient level data recording tool. It is a source of individual level patient data. What was used to abstract this data from the ART follow-up form?
Answer: thank you dear for your comments!

- You are right dear reviewer; the data were collected from the national ART follow-up form after organizing the data collection checklist.
- We will upload the data collection checklist as supplementary material.
- In the revised form of manuscript we already clarifying it.

9. The authors stated that "Patient records that had CD4 cell count measurement less than twice were excluded from the study”. Why was this done? The authors should define the inclusion and exclusion criteria separately.

Answer: thank you dear for your comments!

- To assess the immunological and clinical response of the treatment this study includes only patients who had records of at least two CD4 cell count measurement and WHO-clinical stage.
- In the revised manuscript, we clearly indicated the eligibility criteria.

10. Earlier in the manuscript, it was described that "In this study antiretroviral treatment failure is defined as a clinical failure, an immunological failure, or both". But going through the manuscript, it is evident that CD4 counts (immunologic criteria) were used to determine or confirm treatment failure for all patients. Please ensure consistency of the descriptions throughout the manuscript.

Answer: thank you dear for your comments!

- Yes dear, to define antiretroviral treatment failure both clinical and immunological criteria were used.
- We make a consistent description in the revised form of the manuscript.

11. In the analysis, how was incidence rate measured? It needs description.

Answer: thank you dear for your comments!

- The incidence rate was calculated using person-time of observation.
- It is described in the revised form of manuscript.
12. In the results section, it is mentioned that "Regimen was changed for 576 (56.97%) patients". Is this to describe those who had regimen modification while they were on their first-line regimen?

Answer: thank you dear for your comments!

- This percentage indicates the proportion of patients modified the drug regimen under second-line treatment (after switched to second-line ART).
- We already rephrase it in the revised form of the manuscript.

13. It is also stated that "In the follow-up period, the median survival time of patients on second-line ART was 92 months. This means 50% of clients experienced treatment failure after following for 92 months". Is this a valid interpretation? Is it correct to say it is a median of the survival time? It is known that development of resistance to treatment regimens and failure to ART correlate with duration of treatment. So, for the other 50% clients who have been on second-line regimen in the study follow-up period but didn't have treatment failure in the 92 months, the 'survival time' after this period may be much shorter than 92 months. Or, some clients may continue to be doing well on their second-line regimen for a much longer time. Therefore, would it be still appropriate to use a median time for survival in this scenario?

Answer: thank you!

- You are right dear reviewer! The interpretation of “median survival time” for this study needs revision.
- Now we already revised it in better understanding way and we make highlight for changes.

14. On table2, the person-time is falling dramatically from year-to-year. Who was included in the person-time calculations at each point in time (year)? Were all the 1011 followed from 2008 to 2016 (except those who develop treatment failure on the second line regimen)? Wouldn't the person-time accumulate over the period of the follow-up instead of falling from year to year?

Answer: thank you dear for your comments!
• All the 1,011 study participants didn’t followed from 2008 to 2016. In this study patients were not enrolled at the same time. They have different entry times in the follow-up period.

• The person-time was calculated as follows: First, the baseline time (starting point) was recorded for each study participants. Then, the person time was calculated at specified time (year) intervals for this study. For example in the first year of follow-up, the person year is the sum of the amount individual is observed while without treatment failure.

• Also, in the last row of table two we present the overall person time (the sum of the amount of years each individual is observed while without treatment failure).

15. The incidence at >89 months appears to be higher than at any other time although it was mentioned in the results section that "it was high during the first year of follow up". Please explain.

Answer: thank you dear!

• We make correction; it was high during the first and the last year of follow up period.

• We modified the statement in the revised manuscript.

16. On the predictors of second-line ART failure, "The rate of treatment failure for clients who didn't change the drug regimens during resistance (HR=1.55, 95%CI=1.18, 2.04) was higher by 55%". This is not clear. Is this referring to modification of regimen while these clients were on first-line regimen?

Answer: thank you again!

• No, modified the drug regimen refers after patients switched to second-line ART (second-line regimen modification).

• We already rephrase it in the revised form of manuscript.

17. In the discussion section, it is stated that "In this study, the median time of treatment failure was 13.23 (IQR=7.63, 25.50) months". This is not mentioned in the results section. In addition, how does this relate to the finding that "50% of clients experienced treatment failure after following for 92 months"? It looks like the median time to treatment failure is much longer than 13.23 months. Explain.
Answer: thank you dear for your comments!

- You are right dear reviewer; in the revised form of the manuscript we mentioned the median time of treatment failure in the result section.

- The interpretation of the median survival time is already revised in this way "half of patients didn't have treatment failure in the 92 months after starting second-line treatment”.

- The median time to treatment failure is computed among patients who achieve treatment failure criteria.

18. In the limitations section, it is stated that "Variables such as hemoglobin level, nutritional status, and side effects were some of the plausible factors that were not measured in this study". This is not accurate. The study has in fact included assessments of nutritional status (BMI).

Answer: thank you!

- We make revision in the limitation section.

Reviewer-2

Comments and points raised  Authors response

1. CD4 counts < 100 was seen in 56% cases with failure and 60% in total no. of subjects. Similarly working functional status was also present in similar number of subjects. Kindly explain its association as predictors of failures.

Answer: thank you dear for your relevant comment!

- Off course you are right dear, among the failure group 56.3% of patients were start at CD4 cell count level of below 100 cells/mm3 and 60% in total. But, as presented in “table 1”, among failure group 83.74% of patients were start second-line treatment with working functional status, and in the total 84.67% of were start second-line treatment with working functional status.

- We already describe it in detail in the revised form of the manuscript.
2. Opportunistic infections were found in only small number of cases both in failure group and in total number group. Clinical failure is expected to be associated with opportunistic infections. Kindly explain.

Answer: thank you!

• You are right dear reviewer; clinical failure is highly associated with opportunistic infections.

• However, in this study, the failure group consists of both clinical and immunological failure.

3. P value was not found to be significant for the parameters described in the table 3. Kindly explain.

Answer: thank you again!

• Yes you are right dear reviewer, P value was not found to be significant for the parameters as described in the table 3.

• In Table-3 the proportional hazard assumption was checked by using Schoenfeld residuals. This assumption is supported by an non-significant association between residuals and time.

• We already explained it in the revised form of the manuscript and we make highlight for changes.

4. Discussion-Drug regimen relation and relation of clinical stages to treatment failure were repeated and there was no discussion on these. Kindly do not repeat the results.

Answer: thank you!

• Based on the comment given, we correct it in the revised manuscript.

Thank you!!!