Reviewer’s report

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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Reviewer: Solomon Ahmed

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Review comments

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".

The information on 'response to treatment assessment' is outdated.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.

Describing second line treatment as the last therapeutic option is also not accurate.

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.

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.

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 made a decision of treatment failure independent of what was decided by the ART providers at the facilities. Clarify.
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.

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?

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.

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 count (immunologic criteria) were used to determine or confirm treatment failure for all patients. Please ensure consistency of the descriptions throughout the manuscript.

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

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?

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?

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?

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.
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?

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.

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).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

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Yes

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