Author’s response to reviews

Title: Magnitude and causes of first-line antiretroviral therapy regimen changes among HIV patients in Ethiopia: a systematic review and meta-analysis

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Author’s response to reviews:

Dear editors and reviewers,

Thank you for your letter and for the reviewers’ comments on our manuscript entitled “Magnitude and causes of first line antiretroviral therapy regimen changes among HIV patients in Ethiopia: a systematic review and meta-analysis.” The suggestions offered by the reviewers have been immensely helpful for revising and improving our paper.

We have included the reviewer comments and responded to them point by point, indicating exactly how we addressed each concern and describing the changes we have made. The changes in the revised manuscript are marked in ‘Track changes’ feature. The responses to the reviewers’ comments are provided below.

We would like to express our great appreciation to you and the reviewers for their insightful and constructive comments on our manuscript. We hope the revised manuscript will better suit the BMC Pharmacology and Toxicology and we are happy to consider any further revisions, and we thank you for your continued interest in our research.

Sincerely,

Zerihun Ataro
1. "…ART regimen change is a major challenge for the sustainability of human immunodeficiency virus (HIV) treatment program. This is found to be a major concern among HIV/AIDS patients in a resource limited setting…"
Comment - we need a reference for this concern
★ Response: this sentence is written in the abstract section and we didn’t cite a reference.

2. Objectives - The aim of this review is to generate the best available evidence regarding the magnitude of first line antiretroviral therapy regimen change and the causes for regimen change among HIV patients in Ethiopia

Comment - there is a need to change this to "among HIV patients on ART" in Ethiopia because there is no regimen change among all HIV but for those that are on treatment
★ Response: as suggested by the reviewer the sentences have been changed in the revised manuscript (abstract section, page 2, line 32-33) as follow:

The aim of this review is to generate the best available evidence regarding the magnitude of first-line antiretroviral therapy regimen change and the causes for regimen change among HIV patients on ART in Ethiopia.

3. The estimated national pooled magnitude of regimen change was 37% (95% CI: 34%, 44%); and the major causes identified were toxicity, 58% (95% CI: 46%, 69%); TB co-morbidity, 12% (95% CI: 8%, 16%); treatment failure, 7% (95% CI: 5%, 9%); and pregnancy, 5% (95% CI: 4%, 7%).

Comment - these estimated figures should have a range in bracket because there are 13-22 papers presenting varying switching rates we need to know the minimum and the maximum and then the estimated rate.
★ Response: as suggested by the reviewer, we have included the range in the revised manuscript (Abstract section, page2, line 46-51 and result section, page 11, line 242-244) as follow:

The estimated national pooled magnitude of regimen change was 37% (95% CI: 34%, 44%; Range: 15.1%- 63.8%) with degree of heterogeneity (I2), 98.7%; p-value <0.001. Seventeen articles were used to identify the causes for first line antiretroviral therapy regimen change. The major causes identified were toxicity, 58% (95% CI: 46%, 69%; Range: 14.4%-88.5%); TB co-morbidity, 12% (95% CI: 8%, 16%; Range: 0.8%-31.7%); treatment failure, 7% (95% CI: 5%, 9%; Range: 0.4%-24.4%); and pregnancy, 5% (95% CI: 4%, 7%; Range: 0.6%-11.9%).

4. One-third of HIV patients in Ethiopia changed their first line regimen.

Comments - the question is over what time? A year of starting ART, 2 years, 3 years?
★ Response: most of the included study didn’t mention the period over which the regimen change observed. For those few study who mentioned, the period varies and it is not convenient to state the fixed period for the pooled magnitude.
5. David W Mabirizi, M.D., M.P.H., M.B.A., M.Phil (Reviewer 2):

Comments - correct name David Mabirizi, M.D., M.P.H., M.B.A., M.Phil

6. "The result of this meta-analysis was lower to a study conducted in Europe and North America which reported 40.3% of patients modified first line ART."

Comments - we need to discuss the difference in the rate of switching in studies quoted in Europe, South Africa and Switzerland compared to the rate found in Ethiopia and the possible factors that associated with this difference con rates

★ Response: the possible factors associated with the difference has been included in the revised manuscript (Discussion section, page 13, line 276-281) as follow:
The difference in the rate of regimen change might be due to the difference in socio-demographic characteristics, healthcare systems, variation in defining regimen change and study population. The other possible reasons might be availability viral load testing for monitoring of treatment response might pick regimen change due to virological failure earlier in some countries. Furthermore, limited options of antiretroviral regimen may limit the clinician decision on first line ART regimen change.

8. Comments - Minimize repetitions in the paper
★ Response: The necessary corrections has been made on the revised manuscript

9. This review revealed that one third of HIV patients in Ethiopia changed their first-line regimen which was found to be high.

Comments - The patients do not change their regimen, the regimen is changed by the clinician. Please correct sentence

★ Response: as suggested by the reviewer the sentences have been changed in the revised manuscript (Conclusion section, page 18, line 380-381) as follow:
This review revealed that the original first-line regimen was changed in one-third of HIV patients on ART in Ethiopia, which was found to be high.

Dan Kibuule, PhD (Clinical Pharmacology) (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

It was a pleasure reading this manuscript on the magnitude of changes of ART regimens among HIV patients in Ethiopia. The manuscript is well thought through and has a valid methodology. Nevertheless there are a few issues to address

(1) Kindly specify the MEASURE of magnitude of change (WHAT DOES MAGNITUDE MEAN, % OR)

★ Response: as suggested by the reviewer we have indicated the specific measure of magnitude in the revised manuscript (method section, page 9, line 187-188) as follow:
The number of each case (i.e. first-line regimen change due to any reason) from each article was weighed based on its sample size, pooled and measured using percentage.

(2) Several grammatical errors in the document
★ Response: The grammatical errors are corrected in the revised manuscript

(3) The results of the systematic review not presented, its rather a meta-analysis
★ Response: we have discussed the results from the meta-analysis and included in the revised manuscript

(4) what do these results / findings mean or how will they be implemented. Good results but the significance is not clear given that toxicity, pregnancy and co-morbidity really mean for the HIV/AIDS programme
★ Response: to strengthen the significance of the study, we have included the following paragraph in the revised manuscript (Background section, page 5, line 116-123):
The scaling up of access to ART in Ethiopia brings a complex series of issues; when to initiate therapy, what regimen to use, which drugs within each class, when to change therapy, and which alternative drugs to use. Data on change of highly active antiretroviral therapy provide scientific information for clinicians, policy and decision-makers on the long term strategic approach to initial and subsequent decisions regarding ART. It assists the clinicians to focus on the most effective treatment combinations. Furthermore, it helps to design appropriate measures to increase the duration of original regimen among patients on antiretroviral therapy which subsequently preserve the future treatment options.

(5) Caution should be taken - in use of toxicity (rather Adverse effects should be used) since the grades of toxicity were not highlighted
★ Response: Out of the 17 articles, 12 articles described toxicity, three articles described side effect and only one article describes adverse drug reaction (ADR) as a cause for a regimen change. In this systematic review, we prefer to use the term toxicity since it is mentioned by majority most of the articles included though the toxicity grade was not described.

(6) The study should a high level of heterogeneity; there is need for sub-analyses in the meta-analyses to identify the sources in the heterogeneity (Severity of HIV, facility, ART regimen etc)
★ Response: Exploring the sources of heterogeneity was limited by an insufficient number of the included studies. For example, we planned to perform subgroup analysis by age group, however, only a few studies were carried out with the same age group, which created some difficulties in conducting sub group analysis. Similarly, we were unable to conduct a sub group analysis of other characteristics. This is included in the limitation section of the revised manuscript (page 17, line 372-375).

(7) There is a repetition of results in the discussion
★ Response: the discussion section is modified by including information regarding the implication of the result obtained (Discussion section, page 14, line 296-300; page 15, line 311-314; page 16, line 352-355).

(8) The study ignores the main causes of SWITCHING, i.e. treatment failure (CD4 and VL) sub-analyses should be done
★ Response: We have conducted a separate meta-analysis rather than performing a sub-analysis.

(9) The exact search strategy and criteria used should be included in this paper. In addition what the exact effect sizes measured should be specified.
★ Response: the exact search strategy for Pubmed is described below:
Ovid MEDLINE Search Strategy, Searched on July 9, 2018
Search (((chанг*[Title/Abstract]) OR switсh*[Title/Abstract]) OR shift*[Title/Abstract]) OR modif*
(10) The meta-analyses for TB, pregnancy and toxicity should be done as sub-analyses in the analyses for toxicity and not separately.

Response: All of the mentioned reasons for a regimen change were not described by all of the articles. Furthermore, a single article described many causes which make difficult to arrange the data for sub analysis. Therefore, we prefer to conduct a separate meta-analysis rather than performing a sub-analysis.

(11) studies need to explain the causes of heterogeneity and if we can indeed the findings in this study

Indeed this is a good study BUT the relevance of the findings is not clear. So what? it looks that the findings are in line with recommendations of the ART treatment outcomes. What thresholds of change are recommended. is the threshold high or acceptable?.

Response: the following sentence describing the relevance of the study has been indicated in the revised manuscript (Discussion section page 14, page 296-300) as follow:

Even though the causes for first line ART regimen change are in line with the recommendation of ART treatment outcomes, the rate for ART regimen change were found to be high. This provides important information for clinicians and policymakers in the country as they begin to evaluate and plan for the future needs of the ART treatment program.