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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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

Response to the reviewer’s comments
We would like to thank the reviewers for a careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. The followings are our point-by-point responses:

Amer Hayat Khan, PhD (Reviewer 1):

* Rational of the objective need to elaborate as changing of ART is based on clinical parameters. So why do we need to know and what would be its effect on the treatment outcomes. I will suggest to elaborate and provide more background/rational.

★ Response: as suggested by the reviewer, the following has been included in the background section.

ART regimen is not changed unless absolutely necessary. Once a drug combination is modified, it can no longer be given to the same patient again because it causes significant morbidity and poor quality of life [17]. Most ART programs in low- and middle- income settings follow the World Health Organization (WHO) ART guidelines that emphasize a public health approach to ART delivery [18]. This approach focuses on maximizing survival at the population level through a standardized sequencing of available antiretroviral drugs, delivered to individuals by means of simplified approaches to clinical decision making and basic laboratory monitoring [19].

Changing of ART regimen is based on clinical parameters and the drugs are chosen on the basis of their demonstrated efficacy in suppressing HIV replication and improving survival of PLHA, low cost and wide availability [20]. However, concerns have emerged about the durability, safety, tolerability and rational use of ART regimens. Non-rational use of ART regimen affects the primary goal of ART, i.e suppression of the viral load; restoration and preservation of immunologic function and improved quality of life may not be achieved. It is important to study the long term outcome of the ART regimen used and design strategies that increase the durability of the original regimen.

* What was the Key wording for the data extraction…..?

★ Response: the key wording for the data extraction has been included as follow:

Initial keywords used were: ART, antiretroviral, HAART, chang*, Shift*, Switch*, modif*, substitut*, Ethiopia.
Why outside Ethiopian study were excluded, any rational for that……?

Based on my observation, the study is limited for Ethiopia, then better to publish in some Ethiopian medical journal where local people get benefit from this research OR otherwise author has to provide some background/rational that why they selected specific community. While, I will preferred for the 2nd option.

Response: as suggested by the reviewer, we have included the rational why we selected studies only from Ethiopia in the background section of the revised manuscript as follow:

Even though a public health approach ART of WHO guideline has been used in developing countries [18], there is a difference in the implementation of the guideline of ART regimen change, adherence of the ART treatment across different countries. Furthermore, the national guidelines may differ in their choice of the regimens based on the economic status and capacity [21, 22]. This systematic review included studies conducted in Ethiopia with the aim of providing local evidences as per the real setting of the population. This assists the clinicians to focus on the most effective treatment combinations.

David W Mabirizi, M.D., M.P.H., M.B.A., M.Phil (Reviewer 2):

Line 28/29 - "managed disease. However, ART regimen change has become a common phenomenon and limits the treatment option" ……This sentence lacks clarification on how regimen change limits treatment options. Probably a change in use of words is suggested.

Response: as suggested by the reviewer the sentences have been changed as follow:
Antiretroviral therapy (ART) has markedly decreased the morbidity and mortality due to HIV/AIDS. ART regimen change is a major challenge for the sustainability of human immunodeficiency virus (HIV) treatment program.

Line 49/50 - 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%)………there is no mention of the prescriber recommended switch in regimen that is due to a recommendation by the program due to a change in guidelines. Does that mean there was no change in first line regimen recommendation in the period under review? This aspect is not presented in either the findings/results section nor the discussion.

Response: from the different studies included in our systematic review, there was a regimen change by the program due to the national guideline change. We have included this result in the revised manuscript as follow:

The other reasons responsible for the first line ART regimen change were stock out problem, 14% (95% CI: 0%, 29%) and guideline change, 33% (95% CI: 7%, 60%). Out of the 17 articles, stock out problem was reported by 4 articles [21, 22, 25, 33] and national guideline change was reported by four articles and it was due to phasing out of d4T from the NRTI backbone [21, 23, 33, 34].

Line 51 - Conclusions: One-third of HIV patients in Ethiopia changed their first line regimen…….
37% of the patients switching regimens not including by recommendation by physician, this is a high switch rate likely to indicate either poor adherence by patients and this high treatment failure rate or poor compliance to guidelines by prescribers or an indication of high stock out rate. These aspects should be explored or touched upon in the discussion section.

Response: As suggested by the reviewer the following has been included in the discussion section:
This review revealed that 37% of HIV patients were changed their first line regimen. The regimen change mentioned consists of any regimen change, i.e. those recommended by the physicians as well as those due to different causes. Regardless of the cause, a high rate of first line regimen change was reported in this systematic review. This may indicate poor adherence by patients and/or a poor compliance to guidelines by prescribers. Treatment success needs strict lifelong drug adherence and strong guideline compliance in order to achieve potentially lifelong suppression of HIV replication.

Line 64/65 - The number of people enrolled in ART rose from 900 in 2005 to 300,000 in 2010, and the number of facilities providing increased from four in 2003 to 481 in 2009 [4, 5]. ………These figures are more than 10 years old. It is important to include the most recent figures showing the rapid growth of the program in Ethiopia. Ending this story of enrollment falls short of the realistic picture especially in terms of the number of patients currently on ART in Ethiopia by the end of 2018.

Response: We have included the recent figures in the revised manuscript as follow:
The number of people enrolled in ART rose from 900 in 2005 to 300,000 in 2010, and 436,000 in 2017 and the number of facilities providing ART services increased from four in 2003 to 481 in 2009 and 1361 in 2017 [4-6].

Line 67 - "transformed this infection from a fatal to a medically managed disease"……This sentence may mean that fatal diseases are not medically managed or before the advent of ART, HIV was literally not "medically managed". I would prefer a change in use of terms here.

Response: the sentence has been changed in the revised manuscript as follow:
Highly active antiretroviral therapy (HAART) changes HIV/AIDS from diseases with a high mortality rate to manageable chronic diseases by decreasing the progression of AIDS and reducing HIV-related illness and deaths.

Line 205 - The most commonly mentioned causes for first line ART regimen were toxicity, 58% …..this is a high toxicity rate. Some explanation is needed especially from these studies on the reasons why Ethiopia has such high toxicity rate.

Response: as suggested by the reviewer the following explanation has been included in the discussion section of the revised manuscript:
The majority of patients included in the studies used for this systematic review were started stavudin based regimens[23, 28, 30, 33, 35, 38, 40]. Stavudin is known by its high toxicity which is found to be the major reasons for the removal of stavudin from the current regimen and currently new patients with HIV/AIDS are not starting with stavudin containing regimens. Furthermore, the occurrence of high rate toxicities could be attributed to advanced HIV infection indicated by WHO clinical stage. Majority of the patients included in the articles of this SR had advanced disease stage at baseline (indicated by WHO clinical stage III and IV) [33, 35, 38, 40]. Patients with advanced disease stage were more likely to change the initial HAART regimen. Drug toxicity adversely affects quality of life and potential for
optimum adherence. Lack of adherence ultimately leads emergence of resistance to antiretroviral drugs and treatment failure.

Lastly - the discussion needs a lot of strengthening rather than repeating the results presented in the results section. The discussion should highlight some of the issues identified in earlier comments and presented the papers used in the meta-analysis to explain the observations reported

★ Response: as suggested by the reviewer, to strengthen the discussion we have included two paragraphs in the revised manuscript.