

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Sex differences and adverse events of antiretrovirals in people living with HIV/AIDS: a systematic review and meta-analysis protocol
<b>AUTHORS</b>	de Oliveira, Jardel; Alves, Maíra; Lopes, Luis; Iwami, Rodrigo; Motter, Fabiane; Bergamaschi, Cristiane; Silva, Marcus; Itria, Alexander; Scalco, Diogo; Lucio, Donovan; Mazzei, Lauren; Derech, Rodrigo; Pereira, Tiago; Barreto, Jorge; Lopes, Luciane

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Bezabhe, Woldesellassie University of Tasmania, School of Pharmacy and Pharmacology
<b>REVIEW RETURNED</b>	11-Oct-2021

<b>GENERAL COMMENTS</b>	<p>I thank you for the opportunity to review this protocol. This protocol details how authors will perform a review of RCTs that reported adverse drug reactions in women receiving ART. It would be improved further if the authors addressed the following points.</p> <ol style="list-style-type: none"><li>lines 6-7 "de..." needs correction....de incidence of ADR to antiretroviral therapy...</li><li>Page 7, lines 48-49 "Randomized controlled trials, which are the gold standard of design for intervention studies when comparing efficacy and safety." This statement does not make sense.</li></ol> <p>Page 11 lines 11-13- "No limitations will be imposed on the status of publication (e.g., unpublished studies are eligible for inclusion)" The quality of unpublished studies might be poor. I suggest you exclude studies that are not published in peer-reviewed journals. In the same paragraph, it is not clear whether you are going to include studies written in languages other than English ".. the duration of follow up, year of publication of the study, and language)."</p> <p>Are you going to include all publications regardless of language? How is that feasible?</p> <p>page 9 lines 13-20. The primary outcome, hospitalisation, needs to be defined. Duration of a hospital of stays varies, and difficult to combine results without appropriately defining what hospitalisation means as an outcome. This works for disability as the primary outcome. it needs to be defined.</p> <p>Secondary outcomes page 9 lines 34-35 Discontinuation of ART was not defined? What about switching? Switching antiretroviral agents is more common in the management of ADR. I suggest you define switching and include it as your secondary outcome.</p> <p>The review has several limitations. Different adverse drug reactions of antiretroviral therapy occur during ART. This review ignores the timing of ART initiation, and this is an important</p>
-------------------------	---

	<p>limitation. It will not tell when and which adverse drug reaction occurs during treatment. Antiretroviral drugs are usually given in combination, and difficult to ascertain which agent cause the adverse drug reaction. This review did not address this as a limitation. At times, differentiating adverse drug reactions from HIV/AIDS signs and symptoms is difficult. This is also a limitation of reporting adverse drug reactions of antiretrovirals. This study did not include real-world studies that reported adverse drug reactions in patients receiving antiretrovirals. This should be addressed briefly in the protocol.</p>
--	--

<b>REVIEWER</b>	Mutagonda, Ritah Muhimbili University of Health and Allied Sciences, Clinical Pharmacy and Pharmacology
<b>REVIEW RETURNED</b>	26-Oct-2021

<b>GENERAL COMMENTS</b>	<p><b>Abstract:</b> I suggest the rephrase of the aim instead of assessing the incidence of ADR to ART in people living with HIV/AIDS-associated with age or/and sex should be to determine whether there is an association between ADR to ART with age and/or sex.</p> <p>Add a brief description of how you plan to conduct a meta-analysis.</p> <p><b>Introduction:</b> Rephrase 'Understanding the occurrence of ADR in women' to 'Understanding the occurrence of ADR associated with sex either women or men'. Whatever the findings may be either certain ADRs are prevalent in men than women or vice versa, it is still going to be important information for HIV management.</p> <p><b>Methodology</b> Describe the type of participants and not types of studies. Discuss extensively the limitations of this review including the meta-analysis. What tools (software) will be used in data analysis? On the ethics describe whether or not there is a need for ethical approval and if not reasons for exemption.</p> <p><b>Other comments:</b> 1. The authors should consider revising the grammatic issues observed in this protocol. 2. Check paragraph 6 under the introduction section, there is a statement ending with [ref]</p>
-------------------------	--

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Woldesellassie Bezabhe, University of Tasmania

Comments to the Author:

I thank you for the opportunity to review this protocol. This protocol details how authors will perform a

review of RCTs that reported adverse drug reactions in women receiving ART. It would be improved further if the authors addressed the following points.

R.: Thank you, we made sure to review all your suggestions.

1. lines 6-7 "de..." needs correction....de incidence of ADR to antiretroviral therapy...

R.: We corrected all the typos during our revision.

2. Page 7, lines 48-49 "Randomized controlled trials, which are the gold standard of design for intervention studies when comparing efficacy and safety." This statement does not make sense.

R.: Thank you. We changed this sentence.

Page 11 lines 11-13- "No limitations will be imposed on the status of publication (e.g., unpublished studies are eligible for inclusion)" The quality of unpublished studies might be poor. I suggest you exclude studies that are not published in peer-reviewed journals. In the same paragraph, it is not clear whether you are going to include studies written in languages other than English "... the duration of follow up, year of publication of the study, and language)."

Are you going to include all publications regardless of language? How is that feasible?

R.: We are conducting this review following Cochrane's Handbook and it suggests that the search for studies be scrutinized either in indexed or not indexed databases (grey literature) with no language restrictions to decrease the publication bias. We also will summarize the ongoing trials. Pre-print studies will be summarized separately, and we will conduct sensitivity analysis to check the influence on the pooled estimate.

page 9 lines 13-20.

The primary outcome, hospitalisation, needs to be defined. Duration of a hospital of stays varies, and difficult to combine results without appropriately defining what hospitalisation means as an outcome. This works for disability as the primary outcome. it needs to be defined.

R.: Thank you, we made some changes. We will consider incidence of hospitalization since ART usually is conducted in outpatient.

Secondary outcomes page 9 lines 34-35

Discontinuation of ART was not defined? What about switching? Switching antiretroviral agents is more common in the management of ADR. I suggest you define switching and include it as your secondary outcome.

R.: Thank you for you comment but we are not focusing on switching. We included incidence of discontinuation.

The review has several limitations. Different adverse drug reactions of antiretroviral therapy occur during ART. This review ignores the timing of ART initiation, and this is an important limitation. It will not tell when and which adverse drug reaction occurs during treatment. Antiretroviral drugs are usually given in combination, and difficult to ascertain which agent cause the adverse drug reaction. This review did not address this as a limitation. At times, differentiating adverse drug reactions from HIV/AIDS signs and symptoms is difficult. This is also a limitation of reporting adverse drug reactions of antiretrovirals. This study did not include real-world studies that reported adverse drug reactions in patients receiving antiretrovirals. This should be addressed briefly in the protocol.

R.: Thank you. We added a discussion section to further detail the strengths and limitations.

Reviewer: 2

Dr. Ritah Mutagonda, Muhimbili University of Health and Allied Sciences

Comments to the Author:

Abstract:

I suggest the rephrase of the aim instead of assessing the incidence of ADR to ART in people living with HIV/AIDS-associated with age or/and sex should be to determine whether there is an association between ADR to ART with age and/or sex.

R.: Thank you for your suggestion. We rephrased the sentence.

Add a brief description of how you plan to conduct a meta-analysis.

R.: Thank you. We added the description in the protocol.

Introduction:

Rephrase 'Understanding the occurrence of ADR in women' to 'Understanding the occurrence of ADR associated with sex either women or men'. Whatever the findings may be either certain ADRs are prevalent in men than women or vice versa, it is still going to be important information for HIV management.

R.: Thank you for your suggestion. We rephrased it.

Methodology

Describe the type of participants and not types of studies.

R.: We corrected this section.

Discuss extensively the limitations of this review including the meta-analysis.

R.: We included a discussion section explaining the potential limitations of this review.

What tools (software) will be used in data analysis?

R.: For all analyses, we will use Stata 16 (College Station, TX, USA) and MultiBUGS 2.0 (Cambridge, UK).

On the ethics describe whether or not there is a need for ethical approval and if not reasons for exemption.

R.: The systematic review does not require any ethical approval. However, we plan on submitting the protocol to the ethics committee before the deliberative dialogue.

Other comments:

1. The authors should consider revising the grammatic issues observed in this protocol.

R.: Thank you. We did a major review and corrected the grammatical issues.

2. Check paragraph 6 under the introduction section, there is a statement ending with [ref]

R.: We removed this typo.