

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV in high-income countries: a protocol for an overview of systematic reviews
AUTHORS	Mbuagbaw, Lawrence; Mertz, Dominik; Lawson, Daeria; Smieja, Marek; Benoit, Anita; Alvarez, Elizabeth; Puchalski Ritchie, Lisa; Rachlis, Beth; Logie, Carmen; Husbands, Winston; Margolese, Shari; Thabane, Lehana

VERSION 1 – REVIEW

REVIEWER	Diana M. Sheehan Florida International University, USA
REVIEW RETURNED	09-May-2018

GENERAL COMMENTS	<p>Overall comments: The research question provided by authors would be better answered by doing a systematic review and/or meta-analysis of original research papers. Not enough rationale is provided for why the authors have chosen to do an overview of systematic reviews, and a narrative analysis of the findings. These methodological choices significantly decreases my enthusiasm for the paper, particularly as a “methods” or “protocol” paper is unnecessary in this case.</p> <p>Additionally, retention in care interventions is a rapidly growing field of study. By not including trials that have not already been included in systematic reviews the authors are missing the most up-to-date evidence. This is a significant limitation.</p> <p>Abstract: None.</p> <p>Introduction:</p> <ul style="list-style-type: none"> - Page 6 Line 16: sentence needs reference. - Retention in care has been defined quite extensively in some high income countries including the U.S. as two visits with a care provider (based on appointment dates or laboratory test dates) at least 3 months apart in a given year. It is suggested that the authors revise the paragraph starting in page 7 Line 16 to reflect this. This paragraph needs a deeper understanding of the literature. - Page 7 Line 31: the focus on Canada is presented too late and not reflected in the abstract of the paper. - Page 8 Line 38: sentence needs references. - The authors state that there are some effective interventions, but few that are scalable and even fewer that have been conducted among high-risk populations, and in high income countries. If so, why do the author expect to find systematic reviews that include these studies? How will the authors answer their research question? It seems like the authors already know the answer. - Objective two should include retention in care. <p>Methods:</p>
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	<p>- It is unclear why only including systematic reviews?</p> <p>- If a systematic review is included, will all the studies from that systematic review be included in the present review? Or just the studies with a “randomized comparison”?</p> <p>- A more comprehensive list of terms for retention in care are needed.</p> <p>- Provide rationale for why efficacy will be measured with both adherence and retention improvement and a clinical/laboratory improvement. While this is the aim of all intervention and a good criteria, what will be done with studies that did not assess a clinical/laboratory outcome?</p> <p>Strengths and limitations:</p> <p>- Retention in care interventions is a rapidly growing field of study. By not including trials that have not already been included in systematic reviews the authors are missing the most up-to-date evidence. This is a significant limitation.</p> <p>Editorial:</p> <p>1. Line 32: should be “in high income countries.”</p>
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REVIEWER	Siyon Yi, MD, MHSc, PhD KHANA Center for Population Health Research, Cambodia
REVIEW RETURNED	20-May-2018

GENERAL COMMENTS	<p>Summary This paper presents a protocol a systematic review aiming to document effective interventions for improving adherence and retention in HIV care and treatment. Overall, the paper is well prepared and provides important information on the development of an overview of systematic reviews in this important area. I have no comment on how important it is to publish such a paper in a peer-reviewed journal. Further, I wonder why the authors intend to include only systematic reviews of intervention studies, not the studies themselves? This strategy would miss a number of recent intervention studies not included in previous reviews as mentioned in the limitations. I have some comments that may help improve the clarity and completeness of the information in the manuscript.</p> <p>Title: Authors may want to include geographical coverage of the review (e.g., high-income countries).</p> <p>Abstract 1. In Methods and analysis, page 3, lines 30-32: what did “high income” refer to? High-income countries? 2. As indicated in the objective, please provide the populations at high risk for suboptimal adherence and retention in high-income countries covered in this review. 3. Include keywords used for the literature search. 4. Page 4, line 6: Please use consistent term – people living with HIV</p> <p>Article summary: 5. Key message: I am a little bit confused. I understand that what the authors claimed is the key messages from the actual systematic review, but not from this study protocol, which focus on the methodology of the review. 6. Same comments for strengths and limitations of the study.</p> <p>Introduction 7. The authors have nicely provided background information on different aspects of adherence and retention in care and treatment in</p>
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	<p>different contexts. However, the inconsistency in the list of high-risk populations targeted by this study in the objectives and research questions should be revisited.</p> <p>8. I think the part under the subtitle, “Why it is important to do this overview of systematic reviews” should be summarized and integrated with rationales of the study before the objectives.</p> <p>Methods</p> <p>9. How will high-income countries be defined? If possible, include names of the countries in a table summarizing proposed keywords for systematic review search strategy (for interventions, outcomes, study settings, etc.)</p> <p>10. The selection process should be summarized in a flow chart that will also document the number of excluded studies and reasons for exclusion (although no actual numbers is available now).</p> <p>11. Remove ‘and analysis’ from the subtitle “Systematic review selection, data collection and analysis” as you have another subsection “Analysis and interpretation.”</p> <p>12. Line 48: I believe it was a typo – ‘form’ not ‘from.’</p> <p>Discussion</p> <p>13. It would be better if the authors ended the paper with a brief discussion on the importance of the study and how important findings from this review are and would contribute to the literature and inform future program intervention and policy.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
<p><u>Overall</u></p> <p>The research question provided by authors would be better answered by doing a systematic review and/or meta-analysis of original research papers. Not enough rationale is provided for why the authors have chosen to do an overview of systematic reviews, and a narrative analysis of the findings. These methodological choices significantly decreases my enthusiasm for the paper, particularly as a “methods” or “protocol” paper is unnecessary in this case.</p> <p>Additionally, retention in care interventions is a rapidly growing field of study. By not including trials that have not already been included in systematic reviews the authors are missing the most up-to-date evidence. This is a significant limitation.</p>	<p>We have considered this approach. However, this paper is meant to provide a high level overview of the evidence available and the knowledge gaps. Indeed, numerous systematic reviews have been conducted, including some by members of this group. Given the diversity of interventions and populations studied, it is unlikely that a comprehensive meta-analyses would be possible to cover the scope of material we plan to cover. Typically, systematic reviews would report on adherence or retention, but not both. We plan to summarise the evidence from these reviews by exploring the complex relationship between two distinct yet connected outcomes: adherence and retention.</p> <p>We are of the opinion that a protocol paper is a formal commitment to the scientific community, stakeholders and funders to adhere to defined standards of research conduct.</p> <p>As outlined above we feel that an overview of reviews is the best approach given our</p>

	objectives, and while including trials is an optional approach to overviews, we have chosen not to adopt this approach, given that systematic reviews are also published fairly frequently.
<u>Introduction</u> Page 6 Line 16: sentence needs reference.	We have added a reference for this statement. See reference 3.
Retention in care has been defined quite extensively in some high income countries including the U.S. as two visits with a care provider (based on appointment dates or laboratory test dates) at least 3 months apart in a given year. It is suggested that the authors revise the paragraph starting in page 7 Line 16 to reflect this. This paragraph needs a deeper understanding of the literature.	We agree that there are many definitions of retention in care, but none of them is universally accepted, with a variety of definitions applied in the literature to date. We have reported some of these in the paragraph, and clarified that we will be bound by the definitions provided by the authors of the included systematic reviews. See page 12, lines 2 and 3.
Page 7 Line 31: the focus on Canada is presented too late and not reflected in the abstract of the paper.	In the “ethics and dissemination” section of the abstract we outline that this work is meant to inform further investigations in Canada. See page 4, line 2.
Page 8 Line 38: sentence needs references.	We have added a reference for this statement. See references 18, 27, 28 and 29, for lines 12 to 17.
The authors state that there are some effective interventions, but few that are scalable and even fewer that have been conducted among high-risk populations, and in high income countries. If so, why do the authors expect to find systematic reviews that include these studies? How will the authors answer their research question? It seems like the authors already know the answer.	This work will provide a better understanding of the knowledge gaps with respect to what interventions have been tested in high risk populations in high income countries and which of them are effective. Secondly we will explore the reasons why they are not scalable by measuring the levels of pragmatism.
Objective two should include retention in care.	We have rephrased for clarity and included retention. See page 8, line 12.
<u>Methods</u> It is unclear why only including systematic reviews?	This is a protocol for an overview of systematic reviews. The goal is to provide an overarching synthesis of already synthesized evidence. We have provided more details on this in the text and refer the reviewer to the Cochrane Handbook of systematic reviews: Cochrane Handbook for Systematic Reviews of Interventions [www.cochrane-handbook.org]
If a systematic review is included, will all the studies from that systematic review be included in the present review? Or just the studies with a “randomized comparison”?	Only data from studies with a randomized comparison will be included. We have specified this in the text. See page 12, line 19.
A more comprehensive list of terms for retention in care are needed.	We have reported examples of the search terms that will be used. For retention, we have added

	“Retention, dropouts, loss to follow-up, attrition and persistence”. These terms will be exploded during the search. See page 11, lines 6,7.
Provide rationale for why efficacy will be measured with both adherence and retention improvement and a clinical/laboratory improvement. While this is the aim of all intervention and a good criteria, what will be done with studies that did not assess a clinical/laboratory outcome?	We do not think adherence on it's own is a sufficiently robust outcome if it does not lead to clinical or laboratory changes. The retention in care outcome does not require a clinical or laboratory outcome. Studies that do not include a clinical outcome will still be included but considered as indirect evidence. We have reworded the “analysis and interpretation” section to reflect this. See page 13, lines 3,4.
<u>Strengths and limitations</u> Retention in care interventions is a rapidly growing field of study. By not including trials that have not already been included in systematic reviews the authors are missing the most up-to-date evidence. This is a significant limitation.	As an overview the unit of information is the systematic review. Collection data from individual randomized trials is not required. We refer the reviewer to the Cochrane Handbook of systematic reviews: Cochrane Handbook for Systematic Reviews of Interventions [www.cochrane-handbook.org]
<u>Editorial</u> Line 32: should be “in high income countries.”	We have revised the sentence. See page 3, line 12.
Reviewer 2	
<u>Overall</u> This paper presents a protocol a systematic review aiming to document effective interventions for improving adherence and retention in HIV care and treatment. Overall, the paper is well prepared and provides important information on the development of an overview of systematic reviews in this important area. I have no comment on how important it is to publish such a paper in a peer-reviewed journal. Further, I wonder why the authors intend to include only systematic reviews of intervention studies, not the studies themselves? This strategy would miss a number of recent intervention studies not included in previous reviews as mentioned in the limitations. I have some comments that may help improve the clarity and completeness of the information in the manuscript.	We appreciate this comment but do not prefer this approach. Our evidence will be as current as the most recent systematic review we include. More recent evidence will be identified in updates of this overview of systematic reviews. Searching for individual studies is not a requirement for overviews. We refer the reviewer to the Cochrane Handbook of systematic reviews: Cochrane Handbook for Systematic Reviews of Interventions [www.cochrane-handbook.org] We appreciate the comments that would improve clarity and completeness.
<u>Title</u> Authors may want to include geographical coverage of the review (e.g., high-income countries).	We have revised the title to read: Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV in high income countries: a protocol for an overview of systematic reviews
<u>Abstract</u> In Methods and analysis, page 3, lines 30-32: what did “high income” refer to? High-income countries?	We have revised the sentence to read “high-income countries”. See page 3, line 12.
As indicated in the objective, please provide the	We have added this information to the abstract.

populations at high risk for suboptimal adherence and retention in high-income countries covered in this review.	See page 3, line 12-14.
Include keywords used for the literature search.	This would take us over the word count limit for the abstract. We have listed some terms that will be used.
Page 4, line 6: Please use consistent term – people living with HIV	We have revised the manuscript and used “people living with HIV” throughout.
<u>Article summary</u> Key message: I am a little bit confused. I understand that what the authors claimed is the key messages from the actual systematic review, but not from this study protocol, which focus on the methodology of the review.	Editorial has requested that we remove this section.
Same comments for strengths and limitations of the study.	These refer to the strengths and limitations of the protocol.
<u>Introduction</u> The authors have nicely provided background information on different aspects of adherence and retention in care and treatment in different contexts. However, the inconsistency in the list of high-risk populations targeted by this study in the objectives and research questions should be revisited.	We have clarified that the background includes the high-risk populations we identified in the literature, but our objectives include only those known to be of concern in Ontario. See page 8, lines 9, 10. We have revised the order of the high-risk populations so they are more consistent. See page 8, last 4 lines.
I think the part under the subtitle, “Why it is important to do this overview of systematic reviews” should be summarized and integrated with rationales of the study before the objectives.	We have removed the subheading.
<u>Methods</u> How will high-income countries be defined? If possible, include names of the countries in a table summarizing proposed keywords for systematic review search strategy (for interventions, outcomes, study settings, etc.)	We have provided a definition for high income, as per the World Bank. We will not include country names in our search, studies conducted in low/middle income countries or where high income country data cannot be separated out, will be excluded during screening. See page 12, lines 4 and 5.
The selection process should be summarized in a flow chart that will also document the number of excluded studies and reasons for exclusion (although no actual numbers is available now).	A PRISMA flow chart will be included in the final report to illustrate the search and screening process.
Remove ‘and analysis’ from the subtitle “Systematic review selection, data collection and analysis” as you have another subsection “Analysis and interpretation.”	We have removed “analysis” from the subheading “Systematic review selection, data collection and analysis”. It now reads “Systematic review selection and, data collection “
Line 48: I believe it was a typo – ‘form’ not ‘from.’	We have corrected this. See page 11, line 21.
<u>Discussion</u> It would be better if the authors ended the paper with a brief discussion on the importance of the study and how important findings from this review are and would contribute to the literature and inform future program intervention and policy.	In the “ethics and dissemination” section, we have outlined how we will use this information to design a mixed methods study, and inform policy for high risk populations with HIV in high-income countries. See page 14, lines 8-11.

VERSION 2 – REVIEW

REVIEWER	Diana Sheehan Florida International University, USA
REVIEW RETURNED	11-Jul-2018
GENERAL COMMENTS	While the authors had a respond to my previous concerns and suggestions, they did not accurately address my main concern related to doing a review of systematic reviews which is a significant limitation that will prevent the authors from having scientific findings that are useful to other scientists. Their review of systematic reviews does not offer additional insights than the reviews themselves. While they state that systematic reviews are published regularly, this is not accurate. In order to further evaluate the potential usefulness of this study, one would need to know how many systematic reviews will be included and how recent is the most recently published review is.

VERSION 2 – AUTHOR RESPONSE

We respectfully differ with the views of Prof Sheehan. The purpose of our overview of systematic reviews is to inform a mixed methods study by collecting and summarising information from systematic reviews. Its value lies in our ability to provide an overarching view of all the systematic reviews included. Scientists may wish to read many systematic reviews or one overview of systematic reviews addressing the same topic. The choice of topic and approach is based on a recognised need to generate evidence to support practitioners and people living with HIV in Canada. Overviews are a valid form of evidence synthesis that do not require the use of individual trials. We are working closely with guidance from the Cochrane Handbook (Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. Chapter 22: Overviews of reviews). We fear that the reviewer may not be familiar with this resource.

A simple search of PubMed with the terms: systematic review OR metaanalysis AND HIV revealed 2291 articles in the past 5 years, of which 295 were published in 2018 alone. This adds up to about 37 HIV systematic reviews published per month in one database. Systematic reviews are published regularly!

Knowing how many reviews will be included and how recent they are is contrary to the ethos of systematic reviews and research in general. In fact we would cite an excerpt from the Cochrane Handbook (Chapter 2.1 Rationale for protocols), “Publication of a protocol for a review prior to knowledge of the available studies reduces the impact of review authors’ biases, promotes transparency of methods and processes, reduces the potential for duplication, and allows peer review of the planned methods.” It would appear there are no concerns with the planned methods, but rather with the usefulness of the study. In the extremely unlikely event that we find no studies, we would have identified knowledge gaps that would inform future research.