PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Barriers to and enablers of uptake of and adherence to antiretroviral therapy in the context of integrated HIV and tuberculosis treatment among adults in sub-Saharan Africa: a protocol for a systematic literature review
AUTHORS	Momo Kadia, Benjamin; Takah, Noah; Akem Dimala, Christian; Smith, Adrian

VERSION 1 – REVIEW

REVIEWER	Tendesayi Kufa National Institute for Communicable Diseases South Africa
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	Thank you for the opportunity to review this protocol for a systematic review of ART uptake and adherence in the context of TB/HIV integrated care. The protocol is generally well written and reads well. I however feel that there are some methodological issues that need clarification. Mainly the definition of the population and comparison groups if any. More specific comments are listed below Abstract • Introduction- sentence 2: Can the authors state which treatment they are referring to here? I assumed it was ART • Method: Can the authors indicate the population in which the ART uptake will be measured? In the manuscript text they mention adults. I think it needs to be more specific i.e. adults diagnosed with TB and HIV but not previously on ART? Does the order in which the TB or the HIV is diagnosed matter? Will they be measuring uptake and adherence in the same population or uptake in TB patients newly diagnosed with HIV AND adherence in HIV pts on ART but newly diagnosed with TB Strengths and limitations • #4: the second sentence should start with “This” and not “These”. These implies that grey literature and studies in other languages may reduce the variety of barriers and enablers when in fact it’s their exclusion that will. Manuscript text • Introduction- in paragraph 2, the authors state that the data linking TB/HIV integrated care with improved outcomes is robust. I don’t think so. There are many studies and trials that have failed to demonstrate better outcomes with integrated care. It is

	still recommended for its convenience to the patient- see 2013 systematic review by Helena Legido-Quigley et al Research questions • As per my comment on the abstract, can the authors specify the population that will be included? Will you accept studies of patients who are hospitalised or those being care for in communities or primary care? Can they specify elements of the PICO criteria for systematic reviews? For the quantitative papers what will the comparison group be if any Data extraction and synthesis • How are the primary outcomes defined? Some studies of TB/HIV integration will report challenges? What other wording will be acceptable for barrier or facilitator

REVIEWER	Ingrid V. Bassett, MD, MPH Massachusetts General Hospital Boston, MA, USA
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	This manuscript presents a systematic literature review protocol for assessing barriers to and enablers of uptake and adherence to antiretroviral therapy in the setting of integrated HIV/TB treatment among adults in sub-Saharan Africa. The authors propose to review published literature starting from 2004, when WHO issued provisional guidance on collaborative HIV/TB activities. This is in an interesting and relevant topic. Most of my comments relate to ways to improve clarity. 1. It wasn't until page 4, line 9 when "scarce exploration of qualitative data" is mentioned that I understood this study was going to include qual and quant data. This should be made clearer in the abstract. The abstract mentions RCTs and observational studies will be included – this implies quantitative data will be used and its not clear whether solely qualitative studies will be included. 2. Under research objectives – a "meta-analysis of evidence" is mentioned. What pooled estimates would be measured? For what outcomes? Is an estimate of uptake useful for integration overall? Would it need to consider populations (pregnant women vs prisoners for examples?)? Would it need to be compared to an estimate for lack of integrated services to be most relevant? I found the meta-analysis aspect to be underdeveloped. 3. For adherence – will MEMSCAP and other electronic ART adherence data be included? Or only pill count and directly observed therapy? I worry that excluding electronic adherence monitoring will bias toward excluding more recent studies. 4. It could be made clearer how qualitative and quantitative will both be used. Many trials and observational studies of integration report on outcomes like ART adherence, TB treatment completion, and death. There may be regression models with predictors of poor adherence. How would those regression models be used? Would those factors be included as barriers? It was hard to tell how these two different kinds of data (quant and qual) would be integrated.

	Minor point: 1. page 4, line 3 – missing the word “treatment” in the sentence “anti-TB and ART should be continued as IRIS is typically self-limiting”.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Tendesayi Kufa
Institution and Country: National Institute for Communicable Diseases, South Africa
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you for the opportunity to review this protocol for a systematic review of ART uptake and adherence in the context of TB/HIV integrated care. The protocol is generally well written and reads well. I however feel that there are some methodological issues that need clarification. Mainly the definition of the population and comparison groups if any. More specific comments are listed below
Response: Thank you for your kind remarks.
Abstract

- Introduction- sentence 2: Can the authors state which treatment they are referring to here? I assumed it was ART

Response: Thank you for the comment. ‘Treatment’ in sentence 2 of the introduction has been changed to ‘anti-retroviral therapy’

- Method: Can the authors indicate the population in which the ART uptake will be measured? In the manuscript text they mention adults. I think it needs to be more specific i.e. adults diagnosed with TB and HIV but not previously on ART? Does the order in which the TB or the HIV is diagnosed matter? Will they be measuring uptake and adherence in the same population or uptake in TB patients newly diagnosed with HIV AND adherence in HIV pts on ART but newly diagnosed with TB.

Response: Thank you very much for these insightful comments. Indeed, we will review studies reporting on uptake of and adherence to antiretroviral therapy (ART) during integrated care for TB and HIV among adults. These will include studies that involve HIV-infected TB patients initiating ART in integrated care (to identify barriers to and enablers of uptake) and studies involving persons living with HIV/AIDS already on ART who are newly diagnosed with TB (to identify barriers to and enablers of adherence).These details have now been mentioned in the abstract as well as the methods (under selection criteria, page 5, lines 3-5).
Strengths and limitations

- #4: the second sentence should start with “This” and not “These”. These implies that grey literature and studies in other languages may reduce the variety of barriers and enablers when in fact it’s their exclusion that will.

Response: Thank you very much for this. We have carried out the recommended amendment.
Manuscript text

- Introduction- in paragraph 2, the authors state that the data linking TB/HIV integrated care with improved outcomes is robust. I don’t think so. There are many studies and trials that have failed to demonstrate better outcomes with integrated care. It is still recommended for its convenience to the patient- see 2013 systematic review by Helena Legido-Quigley et al

Response: Thank you for raising this point. We agree with you that several studies did not report improved outcomes after integrating TB and HIV services. We have introduced the word ‘considerable’ in place of robust (introduction: page 3, paragraph 2, line 3)
Research questions

- As per my comment on the abstract, can the authors specify the population that will be included? Will you accept studies of patients who are hospitalised or those being care for in communities or primary care? Can they specify elements of the PICO criteria for systematic reviews? For the quantitative papers what will the comparison group be if any

Response: Thank you for this comment. We have amended the abstract accordingly by specifying the study population that will be included. In order to capture a broad range of barriers and enablers, we will include patients who are hospitalised or treated on outpatient basis in communities or primary care settings. We have now included table 2 which shows the elements of the PICOS criteria for the current systematic review.

Data extraction and synthesis

- How are the primary outcomes defined? Some studies of TB/HIV integration will report challenges? What other wording will be acceptable for barrier or facilitator

Response: Thank you for these remarks. We had included synonyms for the terms 'barrier' and 'facilitator' in the search strategy (table 1). Indeed, the table shows that one of the synonyms for 'barrier' is 'challenge'.

Reviewer: 2
Reviewer Name: Ingrid V. Bassett, MD, MPH
Institution and Country: Massachusetts General Hospital, Boston, MA, USA
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
BMJ Open Review
2019-031789

This manuscript presents a systematic literature review protocol for assessing barriers to and enablers of uptake and adherence to antiretroviral therapy in the setting of integrated HIV/TB treatment among adults in sub-Saharan Africa. The authors propose to review published literature starting from 2004, when WHO issued provisional guidance on collaborative HIV/TB activities. This is in an interesting and relevant topic. Most of my comments relate to ways to improve clarity.

Response: Thank you for accepting to review the manuscript.

1. It wasn't until page 4, line 9 when "scarce exploration of qualitative data" is mentioned that I understood this study was going to include qual and quant data. This should be made clearer in the abstract. The abstract mentions RCTs and observational studies will be included – this implies quantitative data will be used and its not clear whether solely qualitative studies will be included.

Response: Thank you for raising this point. We have made the inclusion of both qualitative and quantitative studies clearer in the abstract (page 2, methods lines 2-3)

2. Under research objectives – a "meta-analysis of evidence" is mentioned. What pooled estimates would be measured? For what outcomes? Is an estimate of uptake useful for integration overall? Would it need to consider populations (pregnant women vs prisoners for examples?)? Would it need to be compared to an estimate for lack of integrated services to be most relevant? I found the meta-analysis aspect to be underdeveloped.

Response: Thank you for these remarks. As mentioned under the data extraction section, we have two secondary outcomes: the rate of ART uptake and the rate of adherence to ART. Pooled estimates of these rates will be derived using meta-analysis, depending on whether the studies with uptake and adherence rates are homogenous in terms of the intervention (integrated care), study design, study populations and measures of the outcome. Sensitivity and subgroup analyses shall also be performed where appropriate. These explanations have now been included in the data extraction section, page 6, lines16-20.

3. For adherence – will MEMSCAP and other electronic ART adherence data be included? Or only pill count and directly observed therapy? I worry that excluding electronic adherence monitoring will bias toward excluding more recent studies.
Response: Thank you for this important suggestion. We shall include electronic ART adherence data as well. This has now been included in the methods, page 6 line 14.
4. It could be made clearer how qualitative and quantitative will both be used. Many trials and observational studies of integration report on outcomes like ART adherence, TB treatment completion, and death. There may be regression models with predictors of poor adherence. How would those regression models be used? Would those factors be included as barriers? It was hard to tell how these two different kinds of data (quant and qual) would be integrated.
Response: Many thanks for these important comments. With regards to qualitative studies, we will include those that specifically describe barriers and enablers from the perspectives of providers, patients and other stakeholders involved in the integrated care programme. With regards to quantitative studies, those that investigate factors associated with uptake and/or adherence of ART (using regression models or other methods) in the context of integrated care will be included. Factors that are associated with poor uptake or adherence will be considered as barriers while factors that are associated with good uptake or adherence will be considered as facilitators. Mixed methods studies whose quantitative or qualitative components meet the inclusion criteria will be included. These explanations have now been included in the methods section under selection criteria (page 5, lines 2 to 10) and the 'data extraction and synthesis' section, page 6 lines 3 to 7.

Minor point:
1. page 4, line 3 – missing the word "treatment" in the sentence "anti-TB and ART should be continued as IRIS is typically self-limiting".
Response: Thank you for this comment. The word 'treatment' has now been introduced in this section of the introduction (introduction, page 4, line 5)

VERSION 2 – REVIEW

REVIEWER	Tendesayi Kufa National Institute for Communicable Diseases, South Africa
REVIEW RETURNED	20-Sep-2019

GENERAL COMMENTS	Thank you for the opportunity to review this revised manuscript. It reads much better than the initial version submitted. The authors have done a good job addressing all the comments I had. The authors should add that the study is a systematic review of both qualitative and quantitative studies in the abstract