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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

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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

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Abstract

Introduction: The scale-up of integrated HIV and tuberculosis (TB) care has been an important intervention to curb the burden of HIV and TB co-infection worldwide. Uptake of and adherence to treatment are key determinants of the quality and therapeutic endpoint of this intervention. This study aims to conduct an up-to-date collection and synthesis of evidence on barriers to and facilitators of uptake of and adherence to antiretroviral therapy (ART) during integrated HIV/TB care in sub-Saharan Africa (SSA).

Method: A systematic review of peer-reviewed literature on the uptake of and adherence to ART in the context of integrated therapy for HIV and TB in SSA will be performed. Randomised controlled trials and observational studies will be included. Medline, Popline, Scopus, Embase, Africa journal online and the Cochrane library databases will be searched for relevant studies published from 2004 (when the first set of guidelines on collaborative HIV/TB services were published by the World Health Organisation) onwards. Two authors will independently screen the search output and retrieve full texts of eligible studies. Disagreements between the two authors will be resolved by arbitration by a third author. Data will be abstracted from the eligible studies and an overall qualitative synthesis will be done. The study will be reported as per the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Ethics and dissemination: This study will be a review of the literature and will not involve primary collection of individuals' data. Amendments to the protocol will be documented in the final review. The final study will be published in a peer-reviewed journal and presented at conferences. The review is expected to contribute to the knowledge base of strategies to enhance uptake of and adherence to ART during concurrent treatment for HIV and TB.

Strengths and limitations

1. This review contributes to addressing the crucial lack of data regarding opportunities and barriers for effective ART uptake and adherence in the domain of integrated treatment for HIV and TB in SSA, the region with the greatest burden of HIV/TB co-infection worldwide. Moreover, previous reports in the region generally provide quantitative data on coverage and functionality of integrated care, with little attention towards qualitative data which include major drivers of low quality of integrated care. This review is among the rare reports that seek to address this problem by using a thematic analysis and qualitative synthesis of relevant evidence.
2. This study will employ a systematic and robust approach to fill the knowledge gap in facilitators of uptake of and adherence to ART in integrated HIV/TB care. Consequently, the evidence generated is expected to be of sufficiently high quality to adequately inform practice in SSA.
3. By exploring and synthesizing evidence on a broad range of factors that determine uptake of and adherence to ART during concurrent HIV/TB care, this review will highlight avenues through which HIV treatment outcome during concurrent care for HIV and TB in sub-Saharan African settings could be optimised. Identified strategies could further be adapted to suit specific low-income contexts.

4. We will not include grey literature and studies published in languages other than English. These may reduce the variety of barriers and enablers that could be captured by our research method.

Introduction

Among persons living with HIV/AIDS (PLWHA) in low-income settings, tuberculosis (TB) remains the principal cause of mortality [1–3]. In 2017, PLWHA accounted for 900, 000 (9%) of the estimated 10 million new TB disease cases worldwide [4] and of the 900,000 co-infected patients, up to 300,000 (33.3%) died because of TB [5]. The majority of these co-infected patients reside in sub-Saharan Africa (SSA); according to the World Health Organization (WHO) global TB report of 2018, up to 72% of all patients co-infected with HIV and TB resided in the region [4].

From a therapeutic perspective, low-income settings of SSA have traditionally relied on separate vertical HIV and TB programmes to deliver concurrent HIV and TB care to co-infected patients [6–11]. Based on robust evidence suggesting that better treatment outcomes are observed when both programmes are integrated, the World Health Organisation (WHO) published policy guidelines regarding the integration of HIV and TB services [12]. Various approaches of delivering integrated services have been proposed and vary from having the services within one health facility to a one-stop-shop strategy in which the services are provided as a single package by the same healthcare team [13]. The first set of guidelines on collaborative HIV/TB activities (released in 2004) comprised activities aimed at integrating TB services into HIV care settings with the objective of decreasing the burden of TB in PLWHA and integrating HIV services into TB control programmes with the objective of decreasing the burden of HIV in TB patients[12]. To reduce the burden of TB in PLWHA, WHO recommended intensified TB case-finding, isoniazid preventive therapy and infection control in healthcare settings. To reduce the burden of HIV in TB patients, WHO made an emphasis on HIV counselling and testing and HIV prevention methods for all TB patients, and cotrimoxazole preventive therapy and HIV/AIDS care and support (including ART) for co-infected patients [12]. It is worth mentioning that the initial guidelines were based on incomplete evidence and were therefore meant to serve as provisional guidelines [14].

In 2012, WHO issued a review of the 2004 interim guidelines [14]. Overall, the updated policy employs the same framework as the interim policy but emphasizes on the establishment of mechanisms for delivering integrated HIV/TB care, preferably at the same time and location. The mechanisms are expected to be established within other programmes such as maternal and child health, and prison health services [14]. Furthermore, monitoring and evaluation of activities linked with integrated HIV/TB care are expected to be based on standardized indicators and reporting formats. In this light, it is worth noting that uptake of and adherence to treatment are important indicators of the quality and therapeutic outcomes of integrated care [14]. WHO recommends that HIV-infected TB patients should be initiated on ART irrespective of their CD4 count, as timely initiation of ART during TB therapy has been shown to significantly improve survival [15]. ART should be started within 8 weeks of initiation of anti-TB treatment and in TB patients with a CD4 count of less than 50cells/mm3, ART should be started within 2 weeks after the onset of anti-TB treatment [15–17]. ART is associated with severe adverse events in HIV patients with TB meningitis so ART in these cases should be delayed. In the

event of TB-associated immune reconstitution inflammatory syndrome (IRIS), anti-TB and ART should be continued as IRIS is typically self-limiting [18–20].

Good coordination and effective communication are vital for optimal delivery of the components of integrated care but previous reports from SSA generally provide quantitative data on coverage and functionality of the services, with scarce exploration of qualitative data related to ART uptake and adherence which are important indicators of the success of integrated care. The aim of this study is to comprehensively review the literature and synthesise relevant evidence from which we will discuss means of improving ART uptake and adherence and HIV treatment outcome during integrated HIV/TB care in SSA.

Research questions

1. What are the barriers to uptake of and adherence to ART in integrated care for HIV and TB among adults in SSA?
2. What are the enablers of uptake of and adherence to ART in integrated HIV/TB care among adults in the region?

Research objectives

1. To develop a literature search strategy for the barriers and enablers of uptake of and adherence to ART in the context of integrated HIV/TB care among adults in SSA.
2. To screen all the identified studies in (1) for relevance to the research questions.
3. To critically appraise the literature obtained from objective (2).
4. To extract relevant data from studies in (3) on the barriers and enablers of uptake of and adherence to ART in integrated HIV/TB care among adults in SSA.
5. To conduct a qualitative synthesis and/or a meta-analysis of the evidence obtained in (4)
6. To draw conclusions on the barriers to and enablers of uptake of and adherence to ART in integrated HIV/TB care among adults in SSA.

Methods and analysis

Search strategy

This will be a systematic literature review. Medline, Embase, Cochrane, Popline, Scopus, and Africa journal online databases will be searched extensively to include studies published from 2004 (when WHO first issued recommendations governing integrated HIV/TB care) onwards. A data extraction form and definitions of key terms will be developed to standardise the data collection process. The search terms and their variations that will be used in combination are shown on table 1. Articles retrieved from the search will be saved on Mendeley desktop software. Two investigators will independently screen retrieved titles, abstracts and full texts (including those found in reference lists of relevant articles). In the event of disagreements between the investigators, arbitration will be done by a third investigator.

Table 1 Search strategy for the systematic review

Search #	Search words
1	(Antiretroviral therapy OR ART) AND (Uptake OR start* OR adher* OR compliance)
2	(Integrat* OR joint OR collaborat* OR concurrent) AND (Tuberculosis OR TB) AND (HIV OR AIDS) AND (treat* OR therap* OR care OR service)
3	Barrier OR challenge OR drawback OR limitation
4	Enabl* OR facilitat* OR opportunit* OR driver
5	Sub-Saharan Africa [MeSH]
6	#1 AND #2 AND #3 AND #5
7	#1 AND #2 AND #4 AND #5

Selection criteria

The review will include peer-reviewed quantitative and qualitative studies on uptake of and adherence to ART among patients receiving integrated HIV/TB care in SSA. The studies will include randomised controlled trials and observational studies published in English. Conference abstracts, editorials, letters to the editor, bulletins and grey literature will be excluded. Studies with insufficient data on uptake of and adherence to ART in the context of collaborative HIV and TB services will also be excluded. Figure 1 shows the procedure that will be followed to arrive at the final articles to be reviewed.

Data extraction and synthesis

Two investigators will extract the relevant data from each article included. The extracted data will be saved on a Microsoft Excel 2016 form and subsequently double-checked for accuracy by a third investigator. We will include data on

1. Publication details: first author name, publication year, journal reference, country and place of study, year of study, study design, study area and setting, study population, sample size, characteristics of patients (such as age and sex distribution, WHO stage etc), as well as limitations and strengths of studies.
2. Primary outcomes:
   -barriers to uptake of and adherence to ART in integrated care.
   -facilitators of uptake of and adherence to ART in integrated care.
3. Secondary outcomes: ART uptake (measured as the proportion of those diagnosed and found eligible after screening who initiated ART) and adherence (measured as a ratio of the number of ART doses taken to the number of doses prescribed over a given time period through pill count or directly observed therapy) in integrated care. These outcomes will be reported as the overall mean ART uptake and the overall mean adherence rate reported in eligible studies.

A thematic synthesis approach will be used to analyse and synthesise the extracted data. Two investigators will develop the initial coding framework on Microsoft Excel 2016 by reading through eligible studies to identify the main themes. These themes will be developed from the above-listed outcomes of interest. The coding framework will be progressively amended to incorporate more themes and sub-themes that emerge as each eligible study is reviewed.

The quality of qualitative studies will be graded using the critical appraisal skills program (CASP) checklist (Table 2) [21] while that of interventional and observational studies will be assessed using their respective quality assessment tools as per the National Health Institute (National Heart, Lung, and Blood Institute) [22]. Overall study quality will be rated as good, fair or poor.

Table 2: Critical Appraisal Skills Program (CASP) checklist for quality assessment of qualitative studies

Criteria	Yes	No	Can't tell	Hint	Comments
Section A: are the results of the study valid?					
Was there a clear statement of the aims of the research?				-What was the goal of the research -Why it was thought important -Its relevance	
Is a qualitative methodology appropriate?				-If the research seeks to interpret or illuminate the actions and/or subjective experience of research participants -is qualitative research the right methodology for addressing the research goal	
Is it worth continuing?					
Was the research design appropriate to address the aims of the research?				-If the researcher has justified the research design (e.g. have they discussed how they decided which method to use?)	
Was the recruitment strategy appropriate to the aims of the research?				-if the researcher has explained how the participants were selected -if they explained why the selected participants were the most appropriate to provide access to the type of knowledge sought by the study -if there are any discussions around recruitment (e.g. why some people chose not to take part)	
Was the data collected in a way that addressed the research issue?				-if the setting for the data collection was justified -if it is clear how data were collected (e.g. focus group, semi-structured interview etc.) -if the researcher has justified the methods chosen -if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide) -if methods were modified during the study. If so, has the researcher explained how and why -if the form of data is clear (e.g. tape recordings, video material, notes etc.) -if the researcher has discussed saturation of data	
Has the relationship between researcher and participants been adequately considered?				-if the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location	

	-how the researcher responded to events during the study and whether they considered the implications of any changes in the research design
Section B: what are the results?	
Have ethical issues been taken into consideration?	-if there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained -if the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study) -if approval has been sought from the ethics committee
Was the data analysis sufficiently rigorous?	-if there is an in-depth description of the analysis process -if thematic analysis is used. If so, is it clear how the categories/themes were derived from the data -whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process -if sufficient data are presented to support the findings -to what extent contradictory data are taken into account -whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation
Is there a clear statement of the findings?	-if the findings are explicit -if there is adequate discussion of the evidence both for and against the researcher's arguments -if the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst) -if the findings are discussed in relation to the original research question
Section C: Will the results help locally?	
How valuable is the research?	-if the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy/ or relevant research-based literature) -if they identify new areas where research is necessary -if the researchers have discussed whether or how the findings can be transformed to other populations or considered other ways the research may be used
Overall risk of bias	
Overall rating/comment	

A narrative approach and/or meta-analysis will be used to summarize abstracted data. The final review will be reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (table 3). Important amendments will be documented in the final review.

Table 3 PRISMA-P 2015 checklist for protocol on 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

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NAP
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NAP
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support:			
Sources	5a	Indicate sources of financial or other support for the review	NAP
Sponsor	5b	Provide name for the review funder and/or sponsor	NAP
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NAP
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5
Study records:			
	11a		5

Data management		Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5/6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5/6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NAP
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5/6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5/6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5/6

Patient and public involvement

We anticipate no patient or public involvement in the study.

Conclusion

This systematic review will explore factors that enable and obstruct ART uptake and adherence in integrated HIV/TB care in SSA. The conduct of the review will be in four parts: identification of relevant studies, study inclusion, data extraction and data synthesis. The results of this review may benefit co-infected patients, clinicians and policy makers. The main limitation of the review is that it will not include studies that are not published in English as well as non-randomised trials and this could reduce the range of barriers and facilitators identified. Nonetheless, the study is one of the rare attempts to fill in the alarming lack of data on the subject matter and the quality of included reports will be ascertained using standard tools, which will enable the generation of valid conclusions in the final report.

Declarations

Contributors: BMK: conception and design of the study. FNT, CAD, AS: critical revision of protocol. All authors have read and approved the final manuscript.
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Competing interests: None declared.
Patient consent: Not required
Ethics approval: Not applicable
Acknowledgement: Not applicable

Supplementary files

Figure 1: Flow diagram for identification of studies to be reviewed on uptake of and adherence to ART in the context of integrated HIV and TB care among adults in sub-Saharan Africa.

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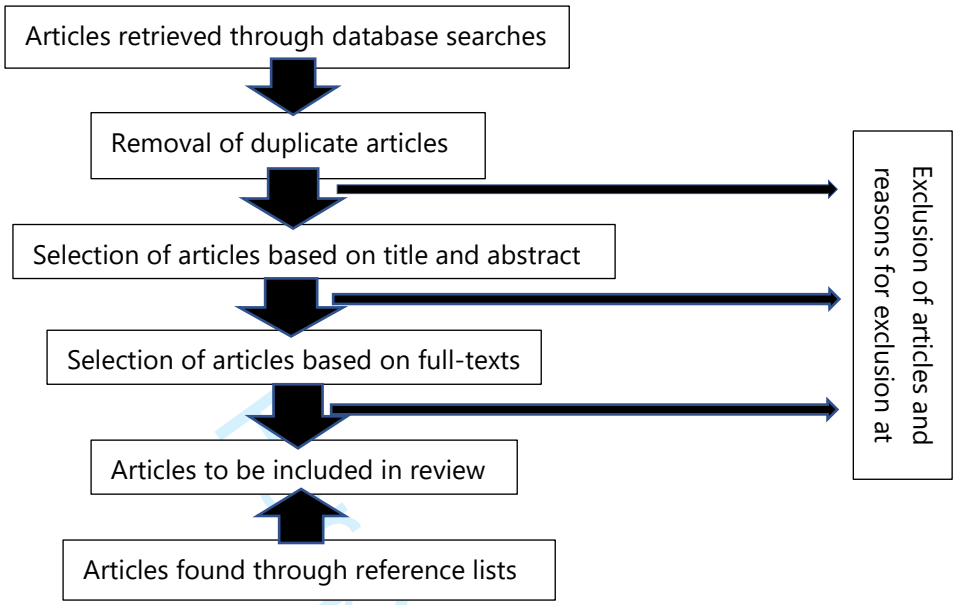

Figure 1: Flow diagram for identification of studies to be reviewed on uptake of and adherence to ART in the context of integrated HIV and TB care in sub-Saharan Africa.

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Abstract

Introduction: The scale-up of integrated HIV and tuberculosis (TB) treatment has been an important intervention to curb the burden of HIV and TB co-infection worldwide. Uptake of and adherence to anti-retroviral therapy (ART) are key determinants of the quality and therapeutic endpoint of this intervention. This study aims to conduct an up-to-date collection and synthesis of evidence on barriers to and facilitators of uptake of and adherence to ART during integrated treatment in sub-Saharan Africa (SSA).

Method: A systematic review of peer-reviewed literature on the uptake of and adherence to ART in the context of integrated therapy for HIV and TB in SSA will be performed. We will review studies reporting on uptake of and adherence to ART during integrated treatment for TB and HIV among adults. These will include studies that involve HIV-infected TB patients initiating ART and studies involving persons living with HIV/AIDS already on ART who are newly diagnosed with TB. Qualitative studies, quantitative studies, randomised trials, and observational studies will be included. Six databases including Medline and Embase will be searched for relevant studies published from March 2004 to July 2019. Two authors will independently screen the search output and retrieve full texts of eligible studies. Disagreements between the two authors will be resolved by arbitration by a third author. Data will be abstracted from the eligible studies and synthesis will be done through descriptive synthesis for qualitative data and meta-analysis for quantitative data.

Ethics and dissemination: This study will be a review of the literature and will not involve primary collection of individuals' data. Amendments to the protocol will be documented in the final review. The final study will be published in a peer-reviewed journal and presented at conferences. The review is expected to contribute to improving strategies to enhance uptake of and adherence to ART in integrated care.

PROSPERO registry: CRD42019131933

Strengths and limitations

1. This study will involve a qualitative synthesis of evidence on antiretroviral treatment (ART) uptake and adherence contrary to previous reports that have tended focus on providing quantitative data on these outcomes of TB/HIV integrated treatment.
2. This review will employ a systematic approach involving a critical appraisal of studies such that the evidence generated is expected to be of sufficiently high quality to adequately inform policy and practice in SSA.
3. Independent reviewing and arbitration by a third reviewer in case of disagreements will reduce the risk of observer bias.
4. By synthesizing evidence on a broad range of drivers of uptake of and adherence to ART, this review will highlight important avenues through which HIV treatment outcome in the context of integrated TB/HIV treatment could be optimised in sub-Saharan Africa. .
5. This review will not include grey literature and studies published in languages other than English and this will contribute to reporting bias.

Introduction

Among persons living with HIV/AIDS (PLWHA) in low-income settings, tuberculosis (TB) remains the principal cause of mortality [1–3]. In 2017, PLWHA accounted for 900, 000 (9%) of the estimated 10 million new TB disease cases worldwide [4] and of the 900,000 co-infected patients, up to 300,000 (33.3%) died because of TB [5]. The majority of these co-infected patients reside in sub-Saharan Africa (SSA); according to the World Health Organization (WHO) global TB report of 2018, up to 72% of all patients co-infected with HIV and TB resided in the region [4].

From a therapeutic perspective, low-income settings of SSA have traditionally relied on separate vertical HIV and TB programmes to deliver concurrent HIV and TB treatment to co-infected patients [6–11]. Based on considerable evidence suggesting that better treatment outcomes are observed when both programmes are integrated, the World Health Organisation (WHO) published policy guidelines regarding the integration of HIV and TB services [12]. Various approaches of delivering integrated services have been proposed and vary from having the services within one health facility to a one-stop-shop strategy in which the services are provided as a single package by the same healthcare team [13]. The first set of guidelines on collaborative HIV/TB activities (released in 2004) comprised activities aimed at integrating TB services into HIV treatment settings with the objective of decreasing the burden of TB in PLWHA and integrating HIV services into TB control programmes with the objective of decreasing the burden of HIV in TB patients[12]. To reduce the burden of TB in PLWHA, WHO recommended intensified TB case-finding, isoniazid preventive therapy and infection control in healthcare settings. To reduce the burden of HIV in TB patients, WHO made an emphasis on HIV counselling and testing and HIV prevention methods for all TB patients, and cotrimoxazole preventive therapy and HIV/AIDS care and support (including ART) for co-infected patients [12]. It is worth mentioning that the initial guidelines were based on incomplete evidence and were therefore meant to serve as provisional guidelines [14].

In 2012, WHO issued a review of the 2004 interim guidelines [14]. Overall, the updated policy employs the same framework as the interim policy but emphasizes on the establishment of mechanisms for delivering integrated HIV/TB treatment, preferably at the same time and location. The mechanisms are expected to be established within other programmes such as maternal and child health, and prison health services [14]. Furthermore, monitoring and evaluation of activities linked with integrated HIV/TB treatment are expected to be based on standardized indicators and reporting formats. In this light, it is worth noting that uptake of and adherence to treatment are important indicators of the quality and therapeutic outcomes of integrated treatment [14]. WHO recommends that HIV-infected TB patients should be initiated on ART irrespective of their CD4 count, as timely initiation of ART during TB therapy has been shown to significantly improve survival [15]. ART should be started within 8 weeks of initiation of anti-TB treatment and in TB patients with a CD4 count of less than 50cells/mm3, ART should be started within 2 weeks after the onset of anti-TB treatment [15–17]. ART is associated with severe adverse events in HIV patients with TB meningitis so ART in these cases should be delayed. In the event of TB-associated immune reconstitution inflammatory syndrome (IRIS), anti-TB treatment and ART should be continued as IRIS is typically self-limiting [18–20].

Good coordination and effective communication are vital for optimal delivery of the components of integrated treatment but previous reports from SSA generally provide quantitative data on coverage and functionality of the services, with scarce exploration of qualitative data related to ART uptake and adherence which are important indicators of the success of integrated treatment. The aim of this study is to comprehensively review the literature and synthesise relevant evidence from which we will discuss means of improving ART uptake and adherence and HIV treatment outcome during integrated HIV/TB treatment in SSA.

Research questions

1. What are the barriers to uptake of and adherence to ART in integrated treatment for HIV and TB among adults in SSA?
2. What are the enablers of uptake of and adherence to ART in integrated HIV/TB treatment among adults in the region?

Research objectives

1. To develop a literature search strategy for the barriers and enablers of uptake of and adherence to ART in the context of integrated HIV/TB treatment among adults in SSA.
2. To screen all the identified studies in (1) for relevance to the research questions.
3. To critically appraise the literature obtained from objective (2).
4. To extract relevant data from studies in (3) on the barriers and enablers of uptake of and adherence to ART in integrated HIV/TB treatment among adults in SSA.
5. To conduct a qualitative synthesis and/or a meta-analysis of the evidence obtained in (4)
6. To draw conclusions on the barriers to and enablers of uptake of and adherence to ART in integrated HIV/TB treatment among adults in SSA.

Methods and analysis

Search strategy

This will be a systematic literature review. Medline, Embase, Cochrane, Popline, Scopus, and Africa journal online databases will be searched extensively to include studies published from 2004 (when WHO first issued recommendations governing integrated HIV/TB treatment) to July 2019. The search terms and their variations that will be used in combination are shown on table 1. Articles retrieved from the search will be saved on Mendeley desktop software. Two investigators will independently screen retrieved titles, abstracts and full texts (including those found in reference lists of relevant articles). In the event of disagreements between the investigators, arbitration will be done by a third investigator.

Table 1 Search strategy for the systematic review

Search #	Search words

1	(Antiretroviral therapy OR ART) AND (Uptake OR start* OR adher* OR compliance)
2	(Integrat* OR joint OR collaborat* OR concurrent) AND (Tuberculosis OR TB) AND (HIV OR AIDS) AND (treat* OR therap* OR care OR service)
3	Barrier OR challenge OR drawback OR limitation
4	Enabl* OR facilitat* OR opportunit* OR driver
5	Sub-Saharan Africa [MeSH]
6	#1 AND #2 AND #3 AND #5
7	#1 AND #2 AND #4 AND #5

Selection criteria

The review will include peer-reviewed quantitative and qualitative studies on uptake of and adherence to ART among patients receiving integrated HIV/TB treatment in SSA. The working definition for integrated treatment will be the delivery of both antiretroviral and anti-tuberculosis drugs to TB/HIV co-infected individuals at the same time and location and by the same provider or healthcare team. Table 2 summarises elements of the selection criteria based on the PICOS (population, intervention, comparison, outcome and study design) criteria.

The review will include randomised trials and observational studies published in English. Mixed methods studies whose quantitative or qualitative components meet the inclusion criteria will be included. Regarding qualitative studies, we will include those that specifically report on barriers and/or enablers. As concerns 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 treatment for TB and HIV will be included. With regards to the study population, we will include studies that involve HIV-infected TB patients initiating ART (to identify barriers to and enablers of uptake) and studies involving PLWHA already on ART who are newly diagnosed with TB and commencing anti-tuberculosis drugs (to identify barriers to and enablers of adherence) within integrated TB/HIV treatment services.

Table 2: Selection criteria for studies to be included in the systematic review

PICOS item	Inclusion criteria	Exclusion criteria
P-population	Studies involving HIV-infected TB patients (adults) initiating ART in integrated care OR adults living with HIV/AIDS already on ART who are newly diagnosed with TB in SSA	Studies involving -Pregnant women and children -Studies conducted out of SSA
I-intervention	Studies on uptake of and adherence to ART in the setting of integrated therapy for TB and HIV.	-Studies describing uptake of and adherence to ART in non-integrated treatment settings -Studies on integrated treatment beyond TB and HIV
C-comparison		

O-outcome(s)	1. Barriers to uptake of and adherence to ART 2. Enablers of uptake of and adherence to ART 3. Rates of uptake of and adherence to ART	Studies that do not describe at least one of: barriers, enablers or determinants of uptake/adherence.
S-study design	Randomised trials, observational studies, quantitative studies and qualitative studies conducted in hospital and community settings.	1) Mini-reviews, editorials, letters to editors, conference abstracts, commentaries, short communications 2) Abstracts whose full data would not be available even upon requesting from the author 3) Unpublished manuscripts and conference abstracts 4) Duplicates studies: for studies published with the same or different titles or in more than one journal, the most updated version shall be considered.

Conference abstracts, editorials, letters to the editor, bulletins and grey literature will be excluded. Studies with insufficient data on uptake of and adherence to ART in the context of collaborative HIV and TB services will also be excluded. Supplementary file 1 shows the procedure that will be followed to arrive at the final articles to be reviewed.

Data extraction and synthesis

Two investigators will extract the relevant data from each article included. A data extraction form and definitions of key terms will be developed to standardise the data collection process. The extracted data will be saved on a Microsoft Excel 2016 form and subsequently double-checked for accuracy by a third investigator. We will include data on

1. Publication details: first author name, publication year, journal reference, country and place of study, year of study, study design, study area and setting, study population, sample size, characteristics of patients (such as age and sex distribution, WHO stage etc), as well as limitations and strengths of studies.
2. Primary outcomes:
   -barriers to uptake of and adherence to ART in integrated care.
   -facilitators of uptake of and adherence to ART in integrated care.
   For qualitative studies, specific barriers and enablers will be extracted as reported in the studies. With regards to quantitative studies investigating factors associated with uptake and/or adherence of ART, 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.
3. Secondary outcomes: ART uptake (measured as the proportion of those diagnosed who initiated ART) and adherence (estimated as the ratio of the number of ART doses taken to the number of doses prescribed over a given time period measured through pill count, directly observed therapy,

electronic data records and other self-reported and objective measures) . These outcomes will be reported as the overall mean ART uptake and the overall mean adherence rate reported in eligible studies. These overall means will be derived from meta-analysis on STATA version 15 to pool the reported estimates on uptake and adherence obtained from eligible studies with the relevant data. The conduct of meta-analysis will depend on whether studies with uptake and adherence rates are generally homogenous in terms of the intervention (integrated treatment), study design, study populations and measures of the outcomes. Because the eligibility criteria for ART initiation are expected to vary with time and setting (during the period under review), we will ascertain that uptake is in accordance with contemporary WHO guidelines in order to avoid heterogeneity in the reporting of uptake (a secondary outcome). When methodological aspects of a study could affect the observed outcome (uptake/adherence) in specific studies, sensitivity analysis that will consist in restricting the meta-analysis to the other studies will be performed. Pooled estimates will be reported on forest plots while risk of publication bias will be assessed by means of funnel plots. Sub-group analyses will be performed where appropriate.

A thematic synthesis approach will be used to analyse and synthesise the extracted data on barriers and enablers. Two investigators will develop the initial coding framework on Microsoft Excel 2016 by reading through eligible studies to identify the main themes. These themes will be developed from the above-listed outcomes of interest. The coding framework will be progressively amended to incorporate more themes and sub-themes that emerge as each eligible study is reviewed.

The quality of qualitative studies will be graded using the critical appraisal skills program (CASP) checklist (Table 3) [21] while that of interventional and observational studies will be assessed using their respective quality assessment tools as per the National Health Institute (National Heart, Lung, and Blood Institute) [22]. For mixed-methods studies, the quality of the qualitative and quantitative components will be assessed using the appropriate tool as described above. Overall study quality will be rated as good, fair or poor. For quantitative evidence, the confidence in the synthesised evidence will be rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. For qualitative evidence, the confidence in the synthesised evidence will be rated using the Grading of Recommendations, Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative Studies (GRADE-CERQUAL).

Table 3: Critical Appraisal Skills Program (CASP) checklist for quality assessment of qualitative studies

Criteria	Yes	No	Can't tell	Hint	Comments
Section A: are the results of the study valid?					
Was there a clear statement of the aims of the research?				-What was the goal of the research -Why it was thought important -Its relevance	
Is a qualitative methodology appropriate?				-If the research seeks to interpret or illuminate the actions and/or subjective experience of research participants -is qualitative research the right methodology for addressing the research goal	

Is it worth continuing?	
Was the research design appropriate to address the aims of the research?	-If the researcher has justified the research design (e.g. have they discussed how they decided which method to use?)
Was the recruitment strategy appropriate to the aims of the research?	-if the researcher has explained how the participants were selected -if they explained why the selected participants were the most appropriate to provide access to the type of knowledge sought by the study -if there are any discussions around recruitment (e.g. why some people chose not to take part)
Was the data collected in a way that addressed the research issue?	-if the setting for the data collection was justified -if it is clear how data were collected (e.g. focus group, semi-structured interview etc.) -if the researcher has justified the methods chosen -if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide) -if methods were modified during the study. If so, has the researcher explained how and why -if the form of data is clear (e.g. tape recordings, video material, notes etc.) -if the researcher has discussed saturation of data
Has the relationship between researcher and participants been adequately considered?	-if the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location -how the researcher responded to events during the study and whether they considered the implications of any changes in the research design
Section B: what are the results?	
Have ethical issues been taken into consideration?	-if there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained -if the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study) -if approval has been sought from the ethics committee
Was the data analysis sufficiently rigorous?	-if there is an in-depth description of the analysis process -if thematic analysis is used. If so, is it clear how the categories/themes were derived from the data

	-whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process -if sufficient data are presented to support the findings -to what extent contradictory data are taken into account -whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation
Is there a clear statement of the findings?	-if the findings are explicit -if there is adequate discussion of the evidence both for and against the researcher's arguments -if the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst) -if the findings are discussed in relation to the original research question
Section C: Will the results help locally?	
How valuable is the research?	-if the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy/ or relevant research-based literature) -if they identify new areas where research is necessary -if the researchers have discussed whether or how the findings can be transformed to other populations or considered other ways the research may be used
Overall risk of bias	
Overall rating/comment	

The final review will be reported as per the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (supplementary file 2). Important amendments will be documented in the final review.

Patient and public involvement

There was no patient or public involvement in the design or planning of the study.

Conclusion

This systematic review will explore factors that enable and obstruct uptake of and adherence to ART when HIV/TB treatment services are integrated in sub-Saharan African settings. The conduct of the review will be in four parts: identification of relevant studies, study inclusion, data extraction and data synthesis. The results of this review will benefit co-infected patients, clinicians and policy makers. The main limitation of the review is that it will not include studies that are not published in

English as well as non-randomised trials and this could reduce the range of barriers and facilitators identified. Nonetheless, the study is one of the rare attempts to fill in the alarming lack of data on the subject matter and the quality of included reports and the confidence in the evidence will be ascertained using standard tools, which will enable the generation of valid conclusions in the final report.

Ethics and dissemination: This study will be a systematic review of the literature and will not involve primary collection of individuals' data. Amendments to the protocol will be documented in the final review. The final study will be published in a peer-reviewed journal and presented at conferences. The review is expected to contribute to the knowledge base of barriers to and enablers of uptake of and adherence to ART during integrated treatment for TB/HIV. Filling this knowledge gap is expected to go a long way to inform policy and practice and improve integrated TB/HIV treatment outcomes in sub-Saharan Africa.

Declarations

Contributors: BMK: conception and design of the study, drafting of the manuscript; NTF: participated in the design of the study, refinement of the literature search strategy and drafting of the protocol; CAD: assisted with the review of the literature and drafting of the initial manuscript; AS: design of the study and formulation the data extraction procedure for outcomes of interest. He reviewed all versions of the manuscript for technical and intellectual consistencies. All authors have read and approved the final manuscript.

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Competing interests: None declared.

Patient consent: Not required

Ethics approval: Not applicable

Acknowledgement: Not applicable

Supplementary files

Supplementary 1: Flow diagram for identification of studies to be reviewed on uptake of and adherence to ART in the context of integrated HIV and TB care among adults in sub-Saharan Africa.

Supplementary file 2: PRISMA-P 2015 checklist for protocol on 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

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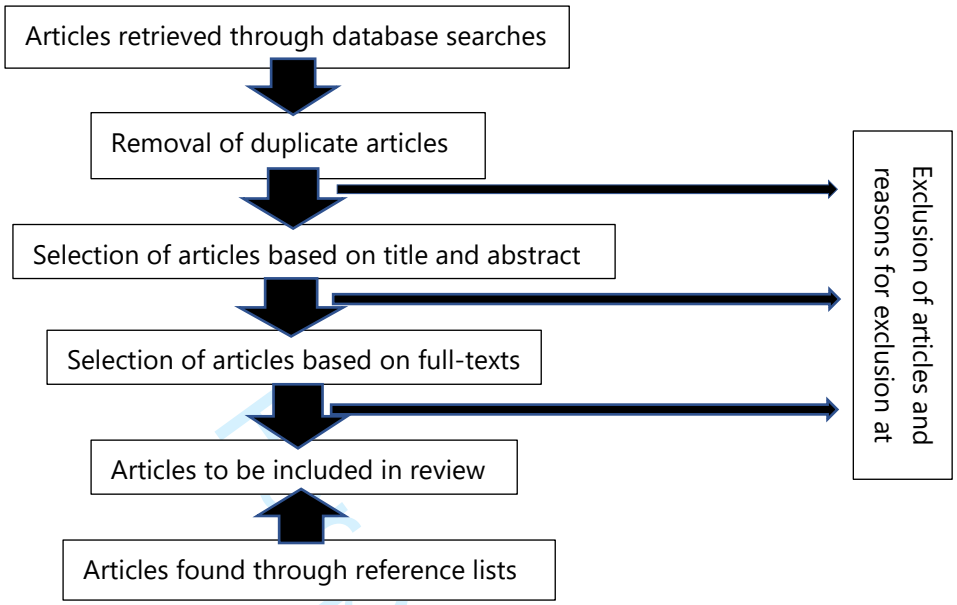

Figure 1: Flow diagram for identification of studies to be reviewed on uptake of and adherence to ART in the context of integrated HIV and TB care in sub-Saharan Africa.

PRISMA-P 2015 checklist for protocol on 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

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NAP
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	9
Support:			
Sources	5a	Indicate sources of financial or other support for the review	NAP
Sponsor	5b	Provide name for the review funder and/or sponsor	NAP
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NAP
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6-7

Continued….

PRISMA-P 2015 checklist for protocol on 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 (continued)

Section and topic	Item No	Checklist item	Page
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7-8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7