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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 Human Immunodeficiency Virus (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 antiretroviral therapy (ART) are key determinants of the quality and therapeutic endpoints 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 in HIV/TB integrated treatment programs 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 qualitative and quantitative studies reporting on the 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 PLWHA 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.

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Strengths and limitations of this study

- This study will involve a qualitative synthesis of evidence on antiretroviral treatment (ART) uptake and adherence contrary to previous reports that have tended to focus on providing quantitative data on outcomes of tuberculosis (TB)/HIV integrated treatment.
- 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 sub-Saharan Africa (SSA).
- Independent reviewing and arbitration by a third reviewer in case of disagreements will reduce the risk of observer bias.
- By synthesising 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 SSA.
- 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

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	Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso ORBurundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad ORComoros OR Congo OR Democratic Republic of Congo OR Djibouti OR Egypt OREquatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR GuineaOR Guinea Bissau OR Ivory Coast OR Cote d'Ivoire OR Jamahiriya OR Jamahiryia ORKenya OR Lesotho OR Liberia OR Libya OR Libia OR Madagascar OR Malawi OR MaliOR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Mocambique ORNamibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR Sao Tome ORSenegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR St HelenaOR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR WesternSahara OR Zaire OR Zambia OR Zimbabwe OR Central Africa OR Central African ORWest Africa OR West African OR Western Africa OR Western African OR East AfricaOR East African OR Eastern Africa OR Eastern African OR North Africa OR NorthAfrican OR Northern Africa OR Northern African OR South African OR SouthernAfrica OR Southern African OR subSaharan Africa OR subSaharan African ORsub-Saharan Africa OR sub-Saharan African
6	#1 AND #2 AND #3 AND #5
7	#1 AND #2 AND #4 AND #5

ART, antiretroviral therapy; TB, tuberculosis.

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 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 antiretroviral treatment (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, the WHO issued a review of the 2004 interim guidelines.[14] Overall, the updated policy employs the same framework as the interim policy but emphasises 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 standardised 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] The 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 50 cells/mm^3, 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 to identify barriers to 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 African journal online databases will be searched extensively to include studies published from 2004 (when the 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 in 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.

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 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 regard 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

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 on requesting from the author 3. Unpublished manuscripts and conference abstracts 4. Duplicate studies: for studies published with the same or different titles or in more than one journal, the most updated version shall be considered.

ART, antiretroviral therapy; PICOS, population, intervention, comparison, outcome and study; SSA, sub-Saharan Africa; TB, tuberculosis.

Table 3 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 (eg, 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 (eg, 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 (eg, focus group, semi-structured interview etc.) ► if the researcher has justified the methods chosen ► if the researcher has made the methods explicit (eg, 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 (eg, 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 (eg, 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	

Continued

Table 3 Continued

Criteria	Yes	No	Can't tell	Hint	Comments
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 (eg, 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 (eg, 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					

CASP, Critical Appraisal Skills Programme.

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.

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. Online 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), as well as limitations and strengths of studies.
2. Primary outcomes:
   a. Barriers to uptake of and adherence to ART in integrated care.
   b. Facilitators of uptake of and adherence to ART in integrated care.
   c. For qualitative studies, specific barriers and enablers will be extracted as reported in the studies. With regard 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 Statistics and Data (STATA) software 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 earlier 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 Programme 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 earlier. 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 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.

The final review will be reported as per the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (online 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 SSA 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 SSA.

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Contributors BMK: conception and design of the study, drafting of the manuscript; NFT: 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 of 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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