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The effects of shifting responsibility from pharmacy to non-pharmacy personnel for dispensing antiretrovirals to patients infected with HIV: A systematic review protocol

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Abstract

Introduction: Critical human resources shortages in low and middle-income countries have been exacerbated by the HIV pandemic as more people become infected and become eligible for antiretroviral therapy. In order to address these human resource constraints, there is a move towards task shifting of responsibilities; including responsibilities for dispensing of antiretrovirals to patients. However, the specifics of task shifting for dispensing of antiretrovirals have not been addressed in a systematic review, yet this is a potential method for improving access to antiretroviral therapy in resource-constrained settings where qualified pharmacists are in short supply.

Methods and analysis: This article describes the protocol for a systematic review to assess the efficacy of task shifting models that use non-pharmacy personnel (i.e. lay people) in dispensing antiretrovirals for treatment of HIV infection. We will search PubMed, CENTRAL, EMBASE, WHO Global Health Library, and relevant grey literature databases for eligible controlled trials and observational studies. We will screen the search output, select eligible studies, and assess the risk of bias and extract data from included studies in duplicate; resolving discrepancies by discussion and consensus. We will perform meta-analysis, investigate clinical and statistical heterogeneity, conduct subgroup and sensitivity analyses, and assess the certainty of the evidence using standard Cochrane methods. This review protocol is registered in the PROSPERO International Prospective Register of Systematic reviews.

Ethics and Dissemination: This being a systematic review in which only published data will be used, ethical review and approval is not required. We will disseminate the review findings in various scientific for a, including peer-reviewed journals. The findings of this review will help inform the development of specifics for task shifting related to dispensing antiretroviral treatment by lay people.

Review registration number: PROSPERO 2015: CRD42015017034

Strengths and Weaknesses

- To our knowledge, this is the first published protocol of a systematic review that will attempt to investigate the effects of task shifting from pharmacy to non-pharmacy personnel for dispensing antiretrovirals to patients infected with HIV.
- The review findings will help inform guidelines from normative agencies such as the World Health Organization.
- The possible weakness of this review would be the limitations of included studies e.g. high risk of biasn and heterogeneity of setting, designs and effects.

Introduction

Description of the condition

Only about 10 million of the close to 30 million people living with HIV who are eligible for antiretroviral therapy (ART) in low and middle income countries are accessing the treatment [1, 2]. Combination ART is effective for minimizing morbidity and mortality among people living with HIV and maximizing their quality of life as well as longevity [3]. Initiating antiretroviral therapy early in the course of the disease has been associated with better health outcomes; and it reduces the risk of transmission to uninfected partners in sero-discordant couples [4]. Surprisingly, most settings with the highest burden of the disease have the least access to care [5]. Although more than five million deaths had been averted up to 2012 in low and middle income countries due to scale up of antiretroviral treatment, bottlenecks to reach universal access to treatment still exist. One of the challenges is the critical shortage of human resources affecting most countries in resource-limited settings. This leaves a substantial shortfall in the number of people living with HIV who currently or shortly will receive antiretroviral treatment. In the United States, the use of multidisciplinary team approach with involvement of pharmacists assuming a central role in the initiation, dispensing and adherence counseling improved treatment outcomes such as viral load, client retention and high likelihood of remaining on therapy [6] but the studies involving pharmacists experienced high costs [6]. For settings where pharmacists are in short supply and resources are limited, task shifting of care to other cadres of health care workers has shown to increase access to initiation of antiretroviral therapy as well as maintenance [7]. The shortage of pharmacy personnel is one of the main reasons most HIV programmes in low and middle income countries, engaged other cadres of health personnel at the on-set of their programme implementation [8, 9]. For example, in Malawi, shifting ART responsibilities to non-physician clinicians and nurses almost doubled patient enrolment to the ART programme [10]. Shifting these responsibilities further to Health Surveillance Assistants (HSAs) and Medical Assistants (MAs) who mainly service health centres resulted in a

majority of ART initiations performed in peripheral health centres. This initiative helped in achieving district wide access to ART [10].

Recently, studies in Uganda, Kenya and Mozambique have shown positive outcomes when non-health professionals (lay people) were used in the delivery of antiretroviral therapy at community level [11]. Even though such community based antiretroviral treatment models are suggested to have potential concerns related to quality of care and stigma, in Mozambique the use of people living with HIV in distributing ARVs, monitoring adherence, reporting outcomes and referring sick patients to health facilities yielded an excellent retention of 97.5% among stable patients on ART [11]. In a cluster randomized trial in Uganda, the use of community health workers who were lay people trained for a few days produced comparable results with the facility-based ART programme in terms of patient retention, viral load suppression, mortality rate and [12]. Similar findings were also obtained in Kenya and some other parts of Uganda when lay people, some of whom were volunteers, were engaged in delivering antiretroviral therapy [12, 13]

Task-shifting has therefore been seen as an achievable solution to the critical human resource shortages affecting scale up of antiretroviral treatment in most African countries [14]. While it is imperative to increase the rate of recruitment and training of health workers as well as improve working conditions to reduce attrition and emigration, the HIV pandemic requires a more urgent measure to address the critical skills shortage, including human resource shortage in non-clinical services domain. The restructuring of the health service model from the traditional doctor-led model to one that allows the introduction of other cadres of health workers has been identified as a way to solve the skills shortage, by reducing the workload on doctors and aiming to reduce the cost of health care [15].

Due to the perceived complexity of the ARVs and as a policy requirement from donor organisations, previously most countries applied the doctor-led model in the management of HIV despite the huge disparity in the doctor: patient ratio in many high burden settings [16]. Several studies conducted in high income settings supported the role of experienced doctors in caring for patients with HIV [17, 18]. Although this may apply in resource rich settings, it does not adequately address the issues facing countries with limited resources and the highest burden of HIV disease. In the settings most affected by HIV, access to HIV treatment needs to be addressed as a priority, and this requires innovative methods to address health worker shortages.

How task shifting using lay people might work

The use of community participation in ART programmes has important implications for health systems. Since huge benefits in terms of reduction in the cost of health services due to minimized utilization of health services have been previously reported [19], community participation therefore has the potential of creating sustainable, cost-

effective and equitable HIV care for people in human resource constrained settings in most parts of the world. Moreover, no significant differences have been reported regarding health outcomes between community ART programmes and facility-based ART programmes [19]. Furthermore, a recent Cochrane review of 10 studies (four randomised controlled trials and six cohort studies) provides evidence of moderate certainty that shifting responsibility from doctors to adequately trained and supported nurses or community health workers for managing HIV patients probably does not decrease the quality of care and, in the case of nurse initiated care, may decrease the numbers of patients lost to follow-up [20].

Why it is important to do this systematic review

The chronic shortage of skilled healthcare workers in low and middle-income countries is a serious obstacle to universal access to antiretroviral therapy. In the Cochrane review referred to above, Kredo and colleagues evaluated the quality of initiation and maintenance of HIV care in models that shift responsibility of care from doctors to non-doctors [20]. One of the 10 included studies, a cluster randomised trial conducted in Uganda, provides moderate certainty evidence that there is little or no difference in health outcomes when specially-trained field workers provide home-based maintenance care and antiretroviral therapy compared to care delivered by doctors in hospitals [12]. A similar trial conducted in Kenya was excluded by Kredo and colleagues because the control arm had little or no access to a doctor. In this study lay people were engaged in antiretroviral therapy produced comparable results with the facility-based ART programme in terms of patient retention, mortality rate and viral load [13]. These two trials are relevant to the important issue of shifting responsibility for antiretroviral dispensing from qualified to less qualified health workers. However, the specifics of task shifting for dispensing of antiretrovirals have not been addressed in a systematic review, yet this is a potential method for improving access to antiretroviral therapy in resource-constrained settings where qualified pharmacists are in short supply; thus the need for the planned review. This will systematically review the scientific literature and assess the efficacy of task shifting models that use lay people in dispensing antiretrovirals for treatment of HIV infection.

Objective

The aim of this review is to systematically review the scientific literature and assess the efficacy of task shifting models that use lay people in dispensing antiretrovirals for treatment of HIV.

Methods

This review has been published in the PROSPERO International Prospective Register of Systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number PROSPERO 2015: CRD42015017034.

Criteria for considering studies for this review

Types of studies

We will include:

- Randomised controlled trials (RCTs), with randomisation at either individual or cluster level.
- Non-randomised controlled trials (non-RCTs), with allocation at either individual or cluster level. Non-RCTs are studies that allocated participants to interventions by alternation between groups, by the use of birth dates or weekdays, or by other non-random methods.
- Interrupted-time-series studies (ITS) and repeated measures studies, with a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention.
- Controlled before-and-after (CBA) studies with a minimum of two intervention and two control sites; comparable timing of the periods of study for the control and intervention groups; and comparability of the intervention and control groups on key characteristics.

We will exclude CBA studies that have only two study locations from the review.

Types of participants

Participants will be HIV infected adults, pregnant and breastfeeding women, adolescents and children receiving antiretroviral treatment.

Types of interventions

We will include interventions in which a model of ART dispensing by lay people (including but not limited to community volunteers, people living with HIV, established community health committees) or another cadre of health workers other than pharmacists or pharmacy technicians was used. This intervention will be compared to dispensing of antiretroviral treatment by pharmacists or pharmacy technicians. We will exclude interventions related to task shifting of selected HIV interventions other than dispensing antiretrovirals such as HIV counseling and testing (HCT) and ART initiation.

Types of outcome measures

Primary outcomes

The primary outcome for this review is mortality.

Secondary outcomes

There are a number of secondary outcome measures which include:

- Virological suppression
- Virological failure

- Number of all-cause sick visits made to the health facility
- Loss to follow-up
- Adherence to ART
- Retention in care after ART initiation where retention is defined by a patient who is still on HIV treatment (assessed at clinically appropriate intervals, e.g. 6, 12, 24, 36, 48, 60 months) and has not (1) died (2) transferred out (3) stopped treatment or (4) been lost-to follow-up. A patient retained in care after ART initiation shall also be defined as someone who has been seen in the clinic at least 6 months later because the WHO recommends an HIV viral load test at 6 months after initiating ART, as well as a CD4 count every six months [21]
- Acceptability to participants (pharmacists and non-pharmacists) and patients
- Feasibility of the intervention.

Search methods for identification of studies

We will perform a comprehensive and exhaustive search of electronic databases and conference proceedings to identify all relevant studies available by 28 February 2015, regardless of language of publication or publication status (published, unpublished, in press and in progress).

Databases of peer-reviewed literature

We will search the following electronic databases, in the period from 1 January 1996 to the search date:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Excerpta Medica Database (EMBASE)
- PubMed
- ISI Web of Science (Science Citation index)
- World Health Organization (WHO) Global Health Library, which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO).

Along with appropriate Medical Subject Heading (MeSH) terms and relevant keywords, we will use the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE [22], and the Cochrane HIV/AIDS Group's validated strategies for identifying references relevant to HIV infection and AIDS. The search strategy will be iterative, in that references of included studies will be searched for additional references. All languages will be included. See Table 1 for our PubMed search strategy, which will be modified and adapted as needed for use in the other databases.

Conference databases

We will search conference abstract archives on the web sites of the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis,

Treatment and Prevention (IAS), for all available abstracts presented at these conferences from 1996 through March 2015.

Searching other resources

In addition to searching electronic databases, we will contact individual researchers, experts working in the field and authors of major trials to address whether any relevant manuscripts are in preparation or in press. The references of published articles found in the above databases will be searched for additional pertinent materials. We will search WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov to identify ongoing trials.

Table 1: Search strategy

PubMed	
#5	#1 AND #2 AND #3 AND #4
#4	(HAART[tiab] OR ART[tiab] OR cART[tiab] OR antiretroviral[tiab] OR anti-retroviral[tiab] OR anti-viral[tiab] OR antiviral[tiab] OR "Antiretroviral Therapy, Highly Active"[Mesh])
#3	(HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or "sexually transmitted diseases, viral"[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]
#2	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[MeSH] OR random allocation[MeSH] OR double-blind method[MeSH] OR single-blind method[MeSH] OR clinical trial[pt] OR clinical trials[MeSH] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp] OR prospective studies[MeSH] OR control*[tw] OR volunteer*[tw]) OR observational[tw] OR non-random*[tw] OR nonrandom*[tw] OR before after study[tw] OR time series[tw] OR cohort*[tw] OR cross-section*[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals[MeSH] NOT human[MeSH])
#1	(task*[tiab] OR task-shifting[tiab] OR referr*[tiab] OR referral and consultation[mh] OR role*[tiab]) AND (health personnel[mh] OR doctor[tiab] OR doctors[tiab] OR clinician[tiab] OR clinicians[tiab] OR physician[tiab] OR physicians[tiab] OR "healthcare provider"[tiab] OR "healthcare providers"[tiab] OR "health care provider"[tiab] OR "health care providers"[tiab] OR pharmac*[tiab] OR apothecar*[tiab] OR chemist*[tiab]

	OR dispensar*[tiab])
Scopus	
	(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TITLE-ABS-KEY (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TITLE-ABS-KEY (ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TITLE-ABS-KEY (RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")
Web of Science	
	(TS=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TS=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TS=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TS=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")) **OR** (TI=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TI=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TI=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART) AND TI=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS"))
CENTRAL	
	HIV* OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME in Title, Abstract, Keywords and (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) in Title, Abstract, Keywords and ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART in Title, Abstract, Keywords

WHO Global Health Library	
	(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*)) AND (HIV* OR human immunodeficiency) AND (antiretroviral OR anti-retroviral))) OR (HIV AND task-shifting) OR (HIV* AND task* AND shift*)

Data collection and analysis

The methodology for data collection and analysis will be based on the guidance of Cochrane Handbook of Systematic Reviews of Interventions[22].

Selection of studies for inclusion

Two authors will read the titles, abstracts and descriptor terms of the downloaded citations to identify potentially eligible reports. We will obtain full text articles for all citations identified as potentially eligible, and two authors will independently inspect these to establish the relevance of the article according to the pre-specified criteria. Where there is uncertainty as to the eligibility of the record, we will obtain and review the full article. Two authors will independently apply the inclusion criteria, and any differences arising will be resolved by discussion with a neutral arbiter. We will review studies for relevance based on design, types of participants and outcome measures.

Data extraction and management

Two authors will independently extract data into a standardised, pre-piloted data extraction form. The following characteristics will be extracted from each included study:

Study details: Complete citation, start and end dates, location, study design characteristics and other relevant details.

Details of the intervention: training of the cadre of health carer that was dispensing; what training or other support or supervision they receive.

Details of the study: Study design; location and time-frame in which it was conducted; type of facility; investigators; other publications associated with the study; funding sources; etc.
Details of participants: Age range, sex, clinical staging, CD4 count, other pertinent details.

Outcome details: Numerators and denominators associated with each outcome; effect estimates provided in papers; definitions of outcomes provided in papers; details of how outcomes were assessed.

Methodological details: Trial design, recruitment, method of randomisation, the numbers of participants entering the trial, trial inclusion and exclusion criteria, length of follow up, losses to follow up, withdrawals or drop-outs.

Bias assessment data: Other details necessary to perform a bias risk assessment using the Cochrane tool described above.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the bias assessment tool described in the Cochrane Handbook [22]. We will resolve any disagreement by discussion or by involving a neutral third party to adjudicate. The Cochrane approach assesses risk of bias in controlled trials across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases [22].

Sequence generation (checking for selection bias)

Low risk: investigators described a random component in the sequence generation process, such as the use of random number table, coin tossing, card or envelope shuffling.

High risk: investigators described a non-random component in the sequence generation process, such as the use of odd or even date of birth, algorithm based on the day or date of birth, hospital or clinic record number.

Unclear risk: insufficient information to permit judgment about the sequence generation process.

Allocation concealment (checking for selection bias)

Low risk: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; or sequentially numbered, opaque, sealed envelopes).

High risk: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule, a list of random numbers), or envelopes were unsealed, non-opaque or not sequentially numbered.

Unclear risk: insufficient information to permit judgment of the allocation concealment or the method not described.

Blinding (checking for performance bias and detection bias)

Low risk: blinding of the participants, key study personnel and outcome assessor and unlikely that the blinding could have been broken. Not blinding in the situation where non-blinding is unlikely to introduce bias.

High risk: no blinding or incomplete blinding when the outcome is likely to be influenced by lack of blinding.

Unclear risk: insufficient information to permit judgment of adequacy or otherwise of the blinding.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

Low risk: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome or missing outcome data balanced in number across groups.

High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data.

Unclear risk: insufficient reporting of attrition or exclusions.

Selective reporting

Low risk: if a protocol is available, primary outcomes in the final trial report correspond closely to those presented in the protocol.

High risk: the primary outcomes differ between the protocol and final trial report.

Unclear risk: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.

Other forms of bias

Low risk: there is no evidence of bias from other sources.

High risk: there is potential bias present from other sources (e.g., early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).

Unclear risk: insufficient information to permit judgment of adequacy or otherwise of other forms of bias.

For blinding and incomplete outcome data, multiple entries can be made if more than one outcome (or time points) is involved. For CBAs and ITS studies, we will assess the risk of bias as follows using the following criteria.

- Was the intervention independent of other changes?
- Was the shape of the intervention effect pre-specified?
- Was the intervention unlikely to affect data collection?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Was the study free from selective outcome reporting?
- Was the study free from other risks of bias?

Each criterion will be scored as 'YES', 'NO', or 'UNCLEAR'. We will consider a CBA or ITS study as having a "low risk of bias" if all the criteria are scored as 'YES'; "moderate risk of bias" if one or more criteria are scored as 'UNCLEAR'; and "high risk of bias" if one or more key criteria are scored as 'NO'. The key criteria will include independence of intervention from other changes, possibility of intervention affecting data collection, completeness of outcome data, and blinding of outcome assessors.

Measures of effect

For randomised controlled trials, we will calculate and present summary statistics for the risk ratio (RR) for dichotomous outcomes and the weighted-mean difference for continuous outcomes, using the 95% confidence interval (CI). We will use the Review Manager 5 software [23] provided by the Cochrane Collaboration for statistical analysis and GRADEpro software [24] to produce GRADE Summary of Findings tables and GRADE evidence profiles. If possible, we will calculate summary statistics using meta-analytic methods. To summarise evidence quality, we will present findings in GRADE Evidence Profiles for all outcomes of interest.

Unit of analysis issues

The unit of analysis will be the individual study participant. Cluster randomised trials will be included in meta-analyses only after adjustments are made for design effect. Design effects for cluster randomised studies will be corrected by using standard procedures, using the formula: design effect = 1 + (m - 1)r, where m is the average cluster size and r is the intra-cluster correlation coefficient (ICC).

Dealing with missing data

We will contact study authors if it is necessary to obtain data missing from published reports.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 >50%), we will explore it by pre-specified subgroup analysis. If heterogeneity persists, we will perform sensitivity analyses, present results separately and propose reasons for the observed heterogeneity.

Assessment of reporting biases

Where we suspect reporting bias we will attempt to contact study authors and ask them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. If any meta-analysis in our review includes 10 more studies, we will assess the potential for publication bias for the studies using a funnel plot [22, 25]. We will attempt to minimise the potential for publication bias through our rigorous review methods and by using our comprehensive search strategy, which includes evaluating published and unpublished literature in all languages.

Data synthesis

We will conduct meta-analysis, if appropriate, using Cochrane's Review Manager software [23]. If heterogeneity between or among studies is low to moderate ($I^2 \leq 50\%$) we will use a fixed effects model. If heterogeneity is high (I^2 >50%) we will use a random effects model. If meta-analysis is not possible, a narrative synthesis of studies will be undertaken. Data will also be presented using the GRADEpro software [24]. GRADE evidence profiles will be generated. We will summarise the quality of

evidence for the studies separately for each outcome for which data are available in GRADE Summary of Findings tables and GRADE evidence profiles [26, 27].

Subgroup analysis

In pooled results with high heterogeneity, we will explore heterogeneity through subgroup analyses of the following: Type of intervention (e.g. cadre of dispensing), comparison group and region (e.g. sub-Saharan Africa, Southeast Asia etc.).

Sensitivity analysis

Where relevant, we will conduct sensitivity analysis to investigate the effect of excluding studies with high or low risk of bias.

Certainty of evidence

We will assess the certainty or quality of evidence across the literature's body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [28], which defines the certainty of evidence for each outcome as "the extent of our confidence that the estimates of effect are correct" [22]. The quality rating across studies has four levels: high, moderate, low or very low. Randomised trials are considered to be of high quality but can be downgraded for any of five reasons; similarly, observational studies are considered to be of low quality, but can be upgraded for any of three reasons. The five factors that can decrease the quality of evidence are: risk of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias. The three factors that can increase the quality level of a body of evidence include: large magnitude of effect, all plausible confounding would reduce a demonstrated effect and the presence of a dose-response gradient.

Reporting of this Review

The findings of this review will be presented in a number of ways. The study selection process will be summarized using a flow diagram; and if we identify 10 or more eligible studies, we will assess publication bias using funnel plots. Where appropriate, we will use the GRADE summary of tables of findings, risk of bias tables or graphs and forest plots. The non-quantitative outcomes will be reported descriptively. A list of both included and excluded studies will be included. The reasons for exclusion will be well summarized.

Ethics and dissemination

Since systematic reviews do not directly involve human participants, they do not require formal ethical clearance [29]. This protocol will be presented at different fora such as systematic review journal clubs and systematic review bursting sessions that are organized in conjunction with the South African Cochrane Centre. In attendance at these meetings are experts in systematic review methodology who will ably provide

the critical appraisal of the methods. The protocol will be approved by the Faculty for Medicine and Health Sciences at Stellenbosch University.

The findings for this review will provide evidence to the World Health Organisation to guide in policy direction as regards to shifting antiretroviral treatment dispensing to lay people. Although, majority of programmes have adopted task shifting in HIV treatment and care at different levels, there has been no policy to guide this practice. We will also publish the findings of this systematic review in peer-reviewed journals and relevant bulletins both at local and international levels.

Declarations of interest

None known.

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External sources:
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Registration	2	PROSPERO 2015: CRD2015017034
Authors:		
Contact	3a	Charles S. Wiysonge. South African Cochrane Centre, South African Medical Research Council, P.O. Box 19070, Tygerberg, 7505, South Africa; Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 241, Cape Town, 8000, South Africa. Email: charlesw@sun.ac.za Dr Tamara Kredo. South African Cochrane Centre, South African Medical Research Council, P.O. Box 19070, Tygerberg, 7505, South Africa; Email: Tamara.kredo@mrc.ac.za Dr Nyanyiwe Mbeye. Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 241, Cape Town, 8000, South Africa. Dr Eyerusalem Negussie. Department of HIV/AIDS, World Health Organization, Geneva, Switzerland. Email: negussiee@who.int Corresponding Author: Dr Nyanyiwe Mbeye, Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 241, Cape Town, 8000, South Africa. Email: nyanyiwembeye@gmail.com
Contributions	3b	CSW, TK and EN conceived the idea; CSW, TK and NMM drafted the protocol. All authors reviewed the protocol and approved the final manuscript. Guarantor: Professor Charles S. Wiysonge

Amendments	4	N/A
Support:		
Sources	5a	South African Medical Research Council Department of HIV/AIDS, World Health Organization, Geneva, Switzerland; Global Health Sciences, University of California, San Francisco, USA Indicate sources of financial or other support for the review
Sponsor	5b	n/a
Role of sponsor or funder	5c	Financial sources have got no role in this review in the development of this review.

INTRODUCTION

Rationale	6	The chronic shortage of skilled healthcare workers in low and middle-income countries is a serious obstacle to universal access to antiretroviral therapy. In the Cochrane review referred to above, Kredo and colleagues evaluated the quality of initiation and maintenance of HIV care in models that shift responsibility of care from doctors to non-doctors. One of the 10 included studies, a cluster randomised trial conducted in Uganda, provides moderate certainty evidence that there is little or no difference in health outcomes when specially-trained field workers provide home-based maintenance care and antiretroviral therapy compared to care delivered by doctors in hospitals. A similar trial conducted in Kenya was excluded by Kredo and colleagues because the control arm had little or no access to a doctor. In this study lay people were engaged in antiretroviral therapy produced comparable results with the facility-based ART programme in terms of patient retention, mortality rate and viral load. These two trials are relevant to the important issue of shifting responsibility for antiretroviral dispensing from qualified to less qualified health workers. However, the specifics of task shifting for dispensing of antiretrovirals have not been addressed in a systematic review, yet this is a potential method for improving access to antiretroviral therapy in resource-constrained settings where qualified pharmacists are in short supply; thus the need for the planned review. This will systematically review the scientific literature and assess the efficacy of task shifting models that use lay people in dispensing antiretrovirals for treatment of HIV infection.

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO): Whether task shifting models that use lay people are efficacious in dispensing antiretroviral treatment to HIV infected adults, pregnant and breastfeeding women, adolescents and children receiving antiretroviral treatment for prevention of mortality compared to use of pharmacy trained personnel.
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 • Randomised controlled trials (RCTs), with randomisation at either individual or cluster level. • Non-randomised controlled trials (non-RCTs), with allocation at either individual or cluster level. Non-RCTs are studies that allocated participants to interventions by alternation between groups, by the use of birth dates or weekdays, or by other non-random methods. • Interrupted-time-series studies (ITS) and repeated measures studies, with a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention. • Controlled before-and-after (CBA) studies with a minimum of two intervention and two control sites; comparable timing of the periods of study for the control and intervention groups; and comparability of the intervention and control groups on key characteristics. • Involving HIV infected adults, pregnant and breastfeeding women, adolescents and children receiving antiretroviral treatment and assessing impact on: o mortality, Virological suppression o Virological failure

		○ Number of all-cause sick visits made to the health facility ○ Loss to follow-up ○ Adherence to ART ○ Retention in care after ART initiation where retention is defined by a patient who is still on HIV treatment (assessed at clinically appropriate intervals, e.g. 6, 12, 24, 36, 48, 60 months) and has not (1) died (2) transferred out (3) stopped treatment or (4) been lost-to follow-up. A patient retained in care after ART initiation shall also be defined as someone who has been seen in the clinic at least 6 months later because the WHO recommends an HIV viral load test at 6 months after initiating ART, as well as a CD4 count every six months ○ Acceptability to participants (pharmacists and non-pharmacists) and patients ○ Feasibility of the intervention.
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: We will search the following sources for articles published between 1996 and March 2015. • Cochrane Central Register of Controlled Trials (CENTRAL) • Excerpta Medica Database (EMBASE) • PubMed • ISI Web of Science (Science Citation index) • World Health Organization (WHO) Global Health Library, which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO). • Conference databases and searching other sources such as contacting individual researchers, experts working in the field and authors of major trials. Additionally, we will use the references of published

		articles found in the above databases. The WHO International Clinical Trials Registry Platform and Clinicaltrials.gov for on-going trials.
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

PubMed	
#5	#1 AND #2 AND #3 AND #4
#4	HAART[tiab] OR ART[tiab] OR cART[tiab] OR antiretroviral[tiab] OR anti-retroviral[tiab] OR anti-viral[tiab] OR antiviral[tiab] OR "Antiretroviral Therapy, Highly Active"[Mesh])
#3	(HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or "sexually transmitted diseases, viral"[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]

	#2	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[MeSH] OR random allocation[MeSH] OR double-blind method[MeSH] OR single-blind method[MeSH] OR clinical trial[pt] OR clinical trials[MeSH] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp] OR prospective studies[MeSH] OR control*[tw] OR volunteer*[tw]) OR observational[tw] OR non-random*[tw] OR nonrandom*[tw] OR before after study[tw] OR time series[tw] OR cohort*[tw] OR cross-section*[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals[MeSH] NOT human[MeSH])
	#1	(task*[tiab] OR task-shifting[tiab] OR referr*[tiab] OR referral and consultation[mh] OR role*[tiab]) AND (health personnel[mh] OR doctor[tiab] OR doctors[tiab] OR clinician[tiab] OR clinicians[tiab] OR physician[tiab] OR physicians[tiab] OR "healthcare provider"[tiab] OR "healthcare providers"[tiab] OR "health care provider"[tiab] OR "health care providers"[tiab] OR pharmac*[tiab] OR apothecar*[tiab] OR chemist*[tiab] OR dispensar*[tiab])
	Scopus	
		(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TITLE-ABS-KEY (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TITLE-ABS-KEY (ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TITLE-ABS-KEY (RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")
	Web of Science	
		(TS=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TS=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TS=(ANTIRETROVIRAL OR ANTI-

	RETROVIRAL OR ART OR CART OR HAART) AND TS=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")) **OR** (TI=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TI=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TI=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART) AND TI=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS"))
CENTRAL	
	HIV* OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME in Title, Abstract, Keywords and (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) in Title, Abstract, Keywords and ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART in Title, Abstract, Keywords
WHO Global Health Library	
	(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*)) AND (HIV* OR human

		immunodeficiency) AND (antiretroviral OR anti-retroviral))) OR (HIV AND task-shifting) OR (HIV* AND task* AND shift*)

Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review This is captured under data extraction and assessment of the risk of bias
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) Two authors will read the titles, abstracts and descriptor terms of the downloaded citations to identify potentially eligible reports. We will obtain full text articles for all citations identified as potentially eligible, and two authors will independently inspect these to establish the relevance of the article according to the pre-specified criteria. Where there is uncertainty as to the eligibility of the record, we will obtain and review the full article. Two authors will independently apply the inclusion criteria, and any differences arising will be resolved by discussion with a neutral arbiter. We will review studies for relevance based on design, types of participants and outcome measures.
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 Two authors will independently extract data into a standardised, pre-piloted data extraction form. Authors will be contacted for missing data.
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 **Study details:** Complete citation, start and end dates, location, study design characteristics and other relevant details.

Details of the intervention: training of the cadre of health carer that was dispensing; what training or other support or supervision they receive.

Details of the study: Study design; location and time-frame in which it was conducted; type of facility; investigators; other publications associated with the study; funding sources; etc.
Details of participants: Age range, sex, clinical staging, CD4 count, other pertinent details.

Outcome details: Numerators and denominators associated with each outcome; effect estimates provided in papers; definitions of outcomes provided in papers; details of how outcomes were assessed.

Methodological details: Trial design, recruitment, method of randomisation, the numbers of participants entering the trial, trial inclusion and exclusion criteria, length of follow up, losses to follow up, withdrawals or drop-outs.

Bias assessment data: Other details necessary to perform a bias risk assessment using the Cochrane tool described above.

Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale

Primary outcomes

Mortality

Secondary outcomes

- Virological suppression
- Virological failure

		• Number of all-cause sick visits made to the health facility • Loss to follow-up • Adherence to ART • Retention in care after ART initiation where retention is defined by a patient who is still on HIV treatment (assessed at clinically appropriate intervals, e.g. 6, 12, 24, 36, 48, 60 months) and has not (1) died (2) transferred out (3) stopped treatment or (4) been lost-to follow-up. A patient retained in care after ART initiation shall also be defined as someone who has been seen in the clinic at least 6 months later because the WHO recommends an HIV viral load test at 6 months after initiating ART, as well as a CD4 count every six months • Acceptability to participants (pharmacists and non-pharmacists) and patients • Feasibility of the intervention.
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

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the bias assessment tool described in the Cochrane Handbook. We will resolve any disagreement by discussion or by involving a neutral third party to adjudicate. The Cochrane approach assesses risk of bias in controlled trials across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases.

Sequence generation (checking for selection bias)

Low risk: investigators described a random component in the sequence generation process, such as the use of random number table, coin tossing, card or

envelope shuffling.

High risk: investigators described a non-random component in the sequence generation process, such as the use of odd or even date of birth, algorithm based on the day or date of birth, hospital or clinic record number.

Unclear risk: insufficient information to permit judgment about the sequence generation process.

Allocation concealment (checking for selection bias)

Low risk: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; or sequentially numbered, opaque, sealed envelopes).

High risk: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule, a list of random numbers), or envelopes were unsealed, non-opaque or not sequentially numbered.

Unclear risk: insufficient information to permit judgment of the allocation concealment or the method not described.

Blinding (checking for performance bias and detection bias)

Low risk: blinding of the participants, key study personnel and outcome assessor and unlikely that the blinding could have been broken. Not blinding in the situation where non-blinding is unlikely to introduce bias.

High risk: no blinding or incomplete blinding when the outcome is likely to be influenced by lack of blinding.

Unclear risk: insufficient information to permit judgment of adequacy or otherwise of the blinding.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

Low risk: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome or missing outcome data balanced in number across groups.

High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data.

Unclear risk: insufficient reporting of attrition or exclusions.

Selective reporting

Low risk: if a protocol is available, primary outcomes in the final trial report correspond closely to those presented in the protocol.

High risk: the primary outcomes differ between the protocol and final trial report.

Unclear risk: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.

Other forms of bias

Low risk: there is no evidence of bias from other sources.

High risk: there is potential bias present from other sources (e.g., early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).

Unclear risk: insufficient information to permit judgment of adequacy or otherwise of other forms of bias.

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised

We will conduct meta-analysis, if appropriate, using Cochrane's Review Manager software. If heterogeneity between or among studies is low to moderate ($I^2 \leq 50\%$) we will use a fixed effects model. If heterogeneity is high ($I^2 > 50\%$) we will use a random effects model. If meta-analysis is not possible, a narrative synthesis of studies will be undertaken. Data will also be presented using the GRADEpro software. GRADE evidence profiles will be generated. We will summarise the quality of evidence for the studies separately for each outcome for which data are available in GRADE Summary of Findings tables and GRADE evidence profiles

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)

For randomised controlled trials, we will calculate and present summary statistics for the risk ratio (RR) for dichotomous outcomes and the weighted-mean difference for continuous outcomes, using the 95% confidence interval (CI). We will use the Review Manager 5 software provided by the Cochrane Collaboration for statistical analysis and GRADEpro software to produce GRADE Summary of Findings tables and GRADE evidence profiles. If possible, we will calculate summary statistics using meta-analytic methods. To summarise evidence quality, we will present findings in GRADE Evidence Profiles for all outcomes of interest.

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity ($I^2 > 50\%$), we will explore it by pre-specified subgroup analysis. If heterogeneity persists, we will perform sensitivity analyses, present results separately and propose reasons for the observed heterogeneity

15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)

		Subgroup analysis In pooled results with high heterogeneity, we will explore heterogeneity through subgroup analyses of the following: Type of intervention (e.g. cadre of dispensing), comparison group and region (e.g. sub-Saharan Africa, Southeast Asia etc.). **Sensitivity analysis** Where relevant, we will conduct sensitivity analysis to investigate the effect of excluding studies with high or low risk of bias.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Narrative review
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Where we suspect reporting bias we will attempt to contact study authors and ask them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. If any meta-analysis in our review includes 10 more studies, we will assess the potential for publication bias for the studies using a funnel plot [22, 25]. We will attempt to minimise the potential for publication bias through our rigorous review methods and by using our comprehensive search strategy, which includes evaluating published and unpublished literature in all languages.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) We will assess the certainty or quality of evidence across the literature's body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [28], which defines the certainty of evidence for each outcome as "the extent of our confidence that the estimates of effect are correct" [22]. The quality rating across studies has four levels: high, moderate, low or very low. Randomised trials are considered to be of high quality but can be downgraded for any of five reasons; similarly, observational studies are considered

to be of low quality, but can be upgraded for any of three reasons. The five factors that can decrease the quality of evidence are: risk of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias. The three factors that can increase the quality level of a body of evidence include: large magnitude of effect, all plausible confounding would reduce a demonstrated effect and the presence of a dose-response gradient.

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

The effects of sharing and shifting tasks from pharmacy to non-pharmacy personnel for providing antiretroviral therapy to people living with HIV: A systematic review protocol

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Complete List of Authors:	MBEYE, NYANYIWE; Stellenbosch University, Centre for Evidence Based Health Care; Cochrane South Africa, South African Medical Research Council Negussie, Eyerusalem; World Health Organisation, Department of HIV/AIDS Kredo, Tamara; South African Medical Research Council, Cochrane South Africa Wiysonge, Charles; Stellenbosch University, Centre for Evidence-Based Health Care; Cochrane South Africa, south african Medical Research Council
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	HIV/AIDS, Health services research
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, task shifting and sharing, antiretroviral therapy, dispensing and distribution, lay providers, pharmacy personnel

The effects of sharing and shifting tasks from pharmacy to non-pharmacy personnel for providing antiretroviral therapy to people living with HIV: A systematic review protocol

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Abstract

Introduction: Critical shortage of human resources for health, in low and middle-income countries have been exacerbated by the HIV pandemic as more people require care including antiretroviral therapy (ART). One of the strategies employed to alleviate the critical shortage of health providers is sharing tasks, including distribution of ARVs to patients, from specialized healthcare providers to health workers with shorter or less formal training. Task shifting and sharing for HIV clinical services has been widely implemented in resource-limited settings, particularly in sub-Saharan Africa. However, the specifics of task-shifting and sharing for dispensing or distribution of antiretroviral drugs from pharmacy personnel to non-pharmacy personnel have not been addressed in a systematic review, yet this can potentially support increasing access to ART. We will assess the effects of task-shifting models that use non-pharmacy personnel to provide ART in low and middle-income countries

Methods and analysis: We will search PubMed, CENTRAL, EMBASE, WHO Global Health Library, and relevant grey literature for eligible controlled trials, interrupted time series, and controlled-before-and-after studies. Two authors will screen the search output, select eligible studies, assess the risk of bias and extract data from included studies; resolving discrepancies by discussion and consensus. We will perform meta-analysis using both fixed and random effects models, investigate clinical and statistical heterogeneity, and assess our confidence in the overall evidence using standard Cochrane methods; including GRADE.

Ethics and Dissemination: This is a systematic review in which secondary published or unpublished data will be included. Ethical review and approval is not required. We will disseminate the review findings in various scientific fora, including peer-reviewed journals. The findings of this review may help inform policy makers and programme managers in defining health workers scope of work, and development of global recommendations for task shifting related to distributing ARVs by non-pharmacy personnel.

Review registration number: PROSPERO 2015: CRD42015017034

Key words: Task shifting, task sharing, HIV, antiretroviral therapy, dispensing, distribution, lay providers, pharmacists, pharmacy personnel.

Strengths and Weaknesses

- To our knowledge, this is the first published protocol of a systematic review that will attempt to investigate the effects of task shifting from pharmacy to non-pharmacy personnel for dispensing or distributing antiretroviral therapy to patients living with HIV.
- The review findings will inform ARV guidelines development process by World Health Organization.
- The possible weakness of this review would be the limitations of included studies e.g. high risk of bias and heterogeneity of setting, designs and effects.

Introduction

Description of the condition

By March 2015, 15 million (40.7%) of the estimated 36.9 million people living with HIV (PLHIV) globally, were receiving antiretroviral therapy (ART) in low and middle income countries[1]. Combination ART is effective for reducing HIV related morbidity and mortality as well as preventing HIV transmission[2]. Initiating ART early in the course of HIV infection has been associated with better health outcomes, both at patient and population levels[3,4]. Scale up of ART in low and middle income countries has averted more than five million deaths, though bottlenecks to reach universal access to ART still exist. One challenge is the critical shortage of human resources for health (HRH), including for delivery of essential pharmacy services, particularly where the HIV burden is highest. The World health Organization (WHO) recommends a minimum of 1 pharmacist per 2,300 population[5]. However, several high HIV burden settings are far from meeting this global recommendation. In addition to the absolute shortage of pharmacists and pharmacy technicians, healthcare providers generally tend to concentrate in urban settings, which further aggravates shortage of HRH in rural and remote settings within a country. For instance in South Africa, which is home to the largest number of PLHIV per country, in 2010 only 24% of registered pharmacists were stationed in the public sector where 80% of the population received care[6].

Description of the intervention

Studies and programme reports indicate that involvement of pharmacy personnel in HIV care results in improved patient outcomes. For instance, in United States, the use of multidisciplinary team approach with pharmacists assuming a central role in the initiation, dispensing and adherence counseling improved treatment outcomes such as viral load, patient retention and medication adherence[7].

The scope of work of pharmacy personnel includes supply management; dispensing and distributing medication; promoting adherence; identifying and preventing potential medication-related issues and monitoring and reporting adverse events. In

some settings, programmes considered alternative models of pharmacy services that shift selected tasks from pharmacy personnel to other health workers, including lay providers and PLHIV. Such alternative models could potentially expand the number of health workers involved in ART distribution, adherence counseling and patient education; freeing more time for pharmacy personnel, supports integration of ART in primary care settings, and can minimize the number of ART pick up facility visits and pharmacy queue waiting times for patients[8].

The purpose of this review is to synthesize the evidence for task shifting and sharing in pharmacy services, where non-pharmacy personnel undertake the tasks for ART dispensing and distribution and medication adherence counseling. The main category of pharmacy personnel includes pharmacists and pharmacy technicians. While the pharmacy workforce does not include mid-level technicians, in several resource-limited countries pharmacy technicians are an important part of the workforce. Among 26 surveyed countries in 2011, where pharmacy technicians are part of the HRH, they constitute 10% (Nigeria) to 70% (Pakistan) of the pharmacy workforce[9]. In few countries, the pharmacy workforce may additionally include pharmacy assistants.

How the intervention might work

Within the last decade, several high HIV burden countries adopted task shifting strategies where nurses and non-physician clinicians initiate and maintain ART[10]. Though this has irrefutably expanded access to ART, it is also increasingly essential that the long facility waiting time and frequent facility visits to pick ART are addressed to alleviate the burden of care, both for patients and healthcare providers[11,12].

Recent studies in Uganda, Kenya and Mozambique have shown positive outcomes when non-health professionals (lay people) delivered ART at the community level[13]. In Mozambique the use of PLHIV for distributing ART,, monitoring adherence, reporting outcomes and referring sick patients to health facilities yielded a retention rate of 97.5% among stable patients on ART[13]. In a cluster randomized trial in Uganda, the use of trained community health workers produced comparable results with the facility-based ART programme in terms of patient retention, viral load suppression and mortality rate [14]. Similar findings were also obtained in Kenya and Uganda when lay providers were engaged in ART delivery[14,15].

Task-shifting and sharing has therefore been seen as an achievable solution to the critical human resource shortages for scale up of ART[16]. While it is imperative to increase the rate of recruitment and training of health workers as well as improve working conditions to reduce attrition and emigration, the HIV pandemic requires a more urgent measure to address the critical skills shortage, including human resource shortage in non-clinical services domain[17]. Such measures may include sharing and

shifting tasks from pharmacy to non-pharmacy personnel. Part of the intention is that selected task shifting to non-pharmacy personnel would free more time for pharmacy personnel to focus on more complex activities such as supply management and pharmacovigilance. Furthermore, such alternative models of ART distribution could potentially alleviate facility workload and long patient waiting time to pick up medication, in high volume health facilities.

Why this review is important

Earlier evidence review on task sharing and shifting for ART expansion focused on clinical services where nurses and non-clinician physicians provide care comparable to physicians[10]. Dependence on and shortages of pharmacists are key constraints on ART expansion, but the specifics of task shifting for ART dispensing or distribution from pharmacy to non-pharmacy personnel have not been reviewed systematically. This is potential strategy for improving access to ART in resource-limited settings where pharmacy personnel are in short supply; thus the need for the planned review. We will systematically review the scientific literature and assess the efficacy of task shifting models that use non-pharmacy personnel including lay providers in dispensing or distributing ART and assessing adherence to treatment of HIV infection.

Objective

The aim of this review is to evaluate the efficacy of sharing and shifting roles (such as dispensing and distributing antiretroviral therapy and assessing adherence to treatment) from pharmacists and pharmacy technicians to non-pharmacy personnel.

Methods

This review has been registered in the PROSPERO International Prospective Register of Systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number PROSPERO 2015: CRD42015017034.

Criteria for considering studies for this review

Types of studies

We will include:

- Randomized controlled trials (RCTs), with randomization at either individual or cluster level.
- Non-randomized controlled trials (non-RCTs), with allocation at either individual or cluster level. Non-RCTs are studies that allocated participants to interventions by alternation between groups, by the use of birth dates or weekdays, or by other non-random methods.
- Interrupted-time-series studies (ITS) and repeated measures studies, with a clearly defined point in time when the intervention occurred

- Controlled before-and-after (CBA) studies with comparable timing of the periods of study for the control and intervention groups; and comparability of the intervention and control groups on key characteristics.

Types of participants

Participants will be people living with HIV (PLHIV) receiving antiretroviral therapy (ART).

Types of interventions

We will include interventions that evaluate shifting and sharing of tasks from pharmacy personnel to non-pharmacy personnel with the intention of increasing access and freeing up time of professionally trained health workers to attend to more complex activities. Such tasks may include dispensing and distribution of ART and adherence support. We will exclude interventions related to task shifting of HIV interventions other than dispensing or distribution of ART, such as HIV testing services and clinical tasks related to ART and HIV care.

The cadres of non-pharmacy personnel may include (but not limited to) nurses, non-physician clinicians, lay providers such as patient peer groups, community volunteers, PLHIV, and established community health committees. This will be compared to ARV dispensing provided by pharmacy personnel. The main category of pharmacy personnel includes pharmacists and pharmacy technicians. While the pharmacy workforce does not always include mid-level technicians, in several resource-limited countries pharmacy technicians are an important part of the health workforce. Among 26 surveyed countries in 2011, pharmacy technicians are part of the HRH, and constitute 10% (Nigeria) to 70% (Pakistan) of the pharmacy workforce[9]. In few countries, the pharmacy workforce may additionally include pharmacy assistants.

Types of outcome measures

Primary outcomes

The primary outcome for this review is risk of death at one year.

Secondary outcomes

Our secondary outcome measures include:

- Virological suppression at one year
- Number of all-cause sick visits made to the health facility, including adverse events
- Loss to follow-up at one year
- Adherence to ART (as measured within the study e.g. pill counts, recall methods, digital methods)
- Acceptability to participants (pharmacists and non-pharmacists) and patients
- Harm, including rates of errors.

Search methods for identification of studies

We will perform a comprehensive and exhaustive search of electronic databases and conference proceedings to identify all relevant studies available by the search date, regardless of language of publication or publication status (published, unpublished, in press and in progress).

Databases of peer-reviewed literature

We will search the following electronic databases, in the period from 1 January 1996 to the search date:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Excerpta Medica Database (EMBASE)
- PubMed
- ISI Web of Science (Science Citation index)
- WHO Global Health Library, which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO).

Along with appropriate Medical Subject Heading (MeSH) terms and relevant keywords, we will use the Cochrane Highly Sensitive Search Strategy for identifying reports of randomized controlled trials in MEDLINE[18], and the Cochrane validated strategies for identifying references relevant to HIV infection and AIDS. To identify other study designs, the RCT string will be omitted. The search strategy will be iterative, in that references of included studies will be searched for additional references. All languages will be included. See Table 1 for our provisional search strategy for electronic databases.

Conference databases

We will search conference abstract archives on the web sites of the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), for all available abstracts presented at these conferences from 1996 through the search date.

Searching other resources

We will also search the references of relevant articles as well as WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov.

Table 1: Proposed Search strategy for electronic databases

PubMed	
ID	Search terms
#1	(task*[tiab] OR task-shifting[tiab] OR referr*[tiab] OR referral and consultation[mh] OR role*[tiab]) AND (health personnel[mh] OR doctor[tiab] OR doctors[tiab] OR clinician[tiab] OR clinicians[tiab] OR physician[tiab]

	OR physicians[tiab] OR "healthcare provider"[tiab] OR "healthcare providers"[tiab] OR "health care provider"[tiab] OR "health care providers"[tiab] OR pharmac*[tiab] OR apothecar*[tiab] OR chemist*[tiab] OR dispensar*[tiab])
#2	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[MeSH] OR random allocation[MeSH] OR double-blind method[MeSH] OR single-blind method[MeSH] OR clinical trial[pt] OR clinical trials[MeSH] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp] OR prospective studies[MeSH] OR control*[tw] OR volunteer*[tw]) OR observational[tw] OR non-random*[tw] OR nonrandom*[tw] OR before after study[tw] OR time series[tw] OR cohort*[tw] OR cross-section*[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals[MeSH] NOT human[MeSH])
#3	(HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or "sexually transmitted diseases, viral"[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]
#4	(HAART[tiab] OR ART[tiab] OR cART[tiab] OR antiretroviral[tiab] OR anti-retroviral[tiab] OR anti-viral[tiab] OR antiviral[tiab] OR "Antiretroviral Therapy, Highly Active"[Mesh])
#5	#1 AND #2 AND #3 AND #4
Scopus	
	(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TITLE-ABS-KEY (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TITLE-ABS-KEY (ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TITLE-ABS-KEY (RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")
Web of Science	
	(TS=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TS=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR*

	AND (NURSE* OR PHARMAC*))) AND TS=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TS=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")) **OR** (TI=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TI=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TI=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART) AND TI=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS"))
CENTRAL	
	HIV* OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME in Title, Abstract, Keywords and (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) in Title, Abstract, Keywords and ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART in Title, Abstract, Keywords
WHO Global Health Library	
	(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*)) AND (HIV* OR human immunodeficiency) AND (antiretroviral OR anti-retroviral))) OR (HIV AND task-shifting) OR (HIV* AND task* AND shift*)

Data collection and analysis

We will base the methodology for data collection and analysis on the guidance provided in the Cochrane Handbook of Systematic Reviews of Interventions[18].

Selection of studies for inclusion

Two authors will read the titles, abstracts and descriptor terms of the downloaded citations to identify potentially eligible reports. We will obtain full text articles for all

citations identified as potentially eligible by at least one of the two authors. Two authors will independently inspect these potentially eligible publications to establish the relevance of the article to the review according to the pre-specified criteria regarding study designs, participants, interventions and comparisons and outcome measures.

Data extraction and management

Two authors will independently extract data into a standardized, pre-piloted data extraction form. The following characteristics will be extracted from each included study:

Study details: Complete citations of publications associated with the study, start and end dates, location, study design characteristics, type of facility involved, investigators, funding sources, recruitment, method of randomization, sequence generation, method of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, length of follow up, losses to follow up, withdrawals or drop-outs and other relevant details.

Details of the intervention: training of the cadre of health worker that was dispensing or distributing ART, what training or other support or supervision they received and other relevant details.

Details of participants: Trial inclusion and exclusion criteria, numbers of participants entering the trial, sex, clinical staging, CD4 count and other pertinent details.

Outcome details: Definitions of outcomes, details of how outcomes were assessed, numerators and denominators associated with each outcome, completeness outcome data, effect estimates reported, and other relevant outcome information.

Assessment of risk of bias in included studies

We will use the risk of bias assessment tool described in the Cochrane Handbook [18]. The Cochrane approach assesses risk of bias in controlled trials across seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective outcome reporting and other potential biases [18].

We will resolve any disagreements between the authors conducting duplicate independent screening of search outputs, assessments of study eligibility, extraction of data, and risk of bias assessment by discussion and consensus. Should this fail to resolve the differences, a third author will arbitrate.

Measures of effect

We will calculate and present risk ratios for dichotomous and time-to-event data and mean differences for continuous data with their 95% confidence intervals.

Unit of analysis issues

The unit of analysis will be the individual study participant. Cluster randomized trials will be included in meta-analyses only after adjustments are made for design effect. Design effects for cluster randomized studies will be corrected by using standard procedures, using the formula: design effect = 1 + (m - 1)r, where m is the average cluster size and r is the intra-cluster correlation coefficient.

Dealing with missing data

We will contact study authors if it is necessary to obtain data missing from published reports.

Assessment of heterogeneity

We will assess heterogeneity using both visual and statistical approaches. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 >50%), we will explore it by pre-specified subgroup analysis. If heterogeneity persists, we will perform sensitivity analyses, present results separately and propose reasons for the observed heterogeneity.

Assessment of reporting biases

Where we suspect reporting bias we will attempt to contact study authors and ask them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. If any meta-analysis in our review includes 10 or more studies, we will assess the potential for publication bias for the studies using a funnel plot[19]. We will attempt to minimise the potential for publication bias through our rigorous review methods, which include a comprehensive search strategy for published and unpublished literature in all languages.

Data synthesis

We will conduct meta-analysis, if appropriate, using Cochrane's Review Manager software[20]. If heterogeneity between or among studies is low to moderate ($I^2 \leq 50\%$) we will use a fixed effects model. If heterogeneity is high (I^2 >50%) we will use a random effects model.

Subgroup analysis

In pooled results with substantial heterogeneity (I^2>50%), we will explore the cause of the heterogeneity through subgroup analyses with subgroups defined by type of intervention (e.g. cadre of health provider), comparison group and region of study (e.g. sub-Saharan Africa, Southeast Asia etc.).

Sensitivity analysis

We will conduct sensitivity analysis to investigate the effect of excluding studies with high risk of bias; with a focus on bias introduced by inadequate allocation concealment, inadequate blinding of outcome assessment and substantial losses to follow up.

Certainty of evidence

We will assess the certainty or quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[21], which defines the certainty of evidence for each outcome as "the extent of our confidence that the estimates of effect are correct" [18]. The quality rating across studies has four levels: high, moderate, low or very low. Randomized trials are considered to be of high quality but can be downgraded for any of five reasons; similarly, observational studies are considered to be of low quality, but can be upgraded for any of three reasons. The five factors that can decrease the quality of evidence are: risk of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias. The three factors that can increase the quality level of a body of evidence include: large magnitude of effect, all plausible confounding would reduce a demonstrated effect and the presence of a dose-response gradient.

Reporting of this review

The findings of this review will be presented in a number of ways. The study selection process will be summarized using a flow diagram; and if we identify 10 or more eligible studies, we will assess publication bias using funnel plots. Where appropriate, we will use the risk of bias tables or graphs, forest plots and GRADE summary of findings tables. The non-quantitative outcomes will be reported descriptively. A list of both included and excluded studies will be included. The reasons for exclusion of studies will be summarized using the PRISMA-P guidelines and will report the findings of the review as recommended by the PRISMA statement.

Ethics and dissemination

Since systematic reviews do not directly involve human participants, they do not require formal ethical clearance[22]. This protocol will be presented at different fora such as systematic review journal clubs and systematic review discussion sessions that are organized in conjunction with Cochrane South Africa. In attendance at these meetings are experts in systematic review methodology who will ably provide the critical appraisal of the methods.

We will provide the findings of this review to the World Health Organization, with the hope that they may guide policy recommendations from this normative agency regarding the sharing and shifting of ART dispensing or distribution from pharmacy to non-pharmacy personnel. Although the majority of national programmes in low and middle-income countries have adopted task shifting in ART dispensing and distribution at different levels, there has been no global policy to guide this practice. We will also publish the findings of this systematic review in peer-reviewed journals and relevant bulletins both at local and international levels.

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Contributors

Nyanyiwe M. Mbeye led the development of the protocol, wrote the first draft, coordinated and integrated comments from co-authors and approved the final version for publication. Eyerusalem Negussie, Tamara Kredo, and Charles Wiysonge conceived the study, critically revised successive drafts of the manuscript, and approved the final version for publication. Charles Wiysonge is the guarantor of the manuscript.

Competing interests

No, there are no competing interests.

Provenance and peer review

Not commissioned; externally peer reviewed.

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PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Title: The effects of sharing and shifting tasks from pharmacy to non-pharmacy personnel for providing antiretroviral therapy to people living with HIV: A systematic review protocol

Section and topic	Item No	Checklist item	Page No
Administrative information			
Title:			**1**
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 5
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	13
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7
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	**7-9**
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies	9-10

		(such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
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	9-10
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	10
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
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	10 & 11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-11
	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)	10-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

BMJ Open

The effects of shifting tasks from pharmacy to non-pharmacy personnel for providing antiretroviral therapy to people living with HIV: A systematic review protocol

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The effects of shifting tasks from pharmacy to non-pharmacy personnel for providing antiretroviral therapy to people living with HIV: A systematic review protocol

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Abstract

Introduction: Shifting selected antiretroviral therapy (ART) tasks from specialised healthcare workers to those with shorter or less formal training has been implemented in resource-limited settings to alleviate critical shortages of human resources for health. However, the specifics of shifting ART dispensing from pharmacy to non-pharmacy personnel have not been addressed in a systematic review; yet this can potentially increase access to ART. We will assess the effects of shifting dispensing and distribution of ART and adherence assessment from pharmacy to non-pharmacy personnel in low and middle-income countries.

Methods and analysis: We will search PubMed, CENTRAL, EMBASE, WHO Global Health Library, and relevant grey literature for eligible controlled trials. Two authors will screen the search output, select eligible studies, assess risk of bias and extract data from included studies; resolving discrepancies by discussion and consensus. We will perform meta-analysis using both fixed and random effects models, investigate clinical and statistical heterogeneity, and assess our confidence in the overall evidence using standard Cochrane methods; including GRADE.

Ethics and Dissemination: Only secondary data will be included in this review and ethical approval is not required. We will disseminate the review findings in various scientific fora, including peer-reviewed journals. The findings may help to inform policy makers in defining the scope of work of healthcare workers, and global recommendations for shifting the dispensing and distribution of ART from pharmacy to non-pharmacy personnel.

Review registration: PROSPERO, registration number CRD42015017034

Key words: Task shifting, HIV, antiretroviral therapy, dispensing, distribution, lay providers, pharmacists, pharmacy personnel.

Strengths and Weaknesses

- To our knowledge, this is the first published protocol of a systematic review that will investigate the effects of task shifting from pharmacy to non-pharmacy personnel for dispensing or distributing antiretroviral therapy to patients living with HIV.
- The protocol was written according to the PRISMA-P (Preferred reporting items for systematic review and meta-analysis protocols) recommendations.
- The review findings may help to inform antiretroviral therapy guidelines by the World Health Organization.
- The possible weakness of the planned review would be the limitations of included studies e.g. high risk of bias and heterogeneity of settings, designs and effects.

Introduction

Description of the condition

By March 2015, fifteen million (40.7%) of the estimated 36.9 million people living with HIV (PLHIV) globally were receiving antiretroviral therapy (ART)[1]. Combination ART is effective for reducing HIV related morbidity and mortality as well as preventing HIV transmission[2]. Initiating ART early in the course of HIV infection has been associated with better health outcomes, both at patient and population levels[3,4]. Scale up of ART in low and middle income countries has averted more than five million deaths, however, bottlenecks to reach universal access to ART still exist. One challenge is the critical shortage of human resources for health (HRH), including for delivery of essential HIV related pharmacy services.

The World Health Organization (WHO) recommends a minimum of 1 pharmacist per 2,300 population; but most countries in low-resource settings such as sub-Saharan Africa have not yet met this target[5]. In addition to the absolute shortage, it is likely that there is an uneven distribution of pharmacists in such settings; as is the case with other specialist healthcare workers who tend to concentrate in urban areas and the private sector, further aggravating the HRH shortage[6]. For instance in South Africa, which is home to the largest number of PLHIV in any country in the world, in 2010 only 24% of registered pharmacists were stationed in the public sector where 80% of the population received care[7].

Description of the intervention

Studies and programme reports indicate that involvement of pharmacy personnel in HIV care results in improved patient outcomes. For instance, in the United States, the use of a multidisciplinary team approach with pharmacists assuming a central role in

ART initiation, dispensing and adherence counseling improved treatment outcomes such as viral load, patient retention and medication adherence[8].

The scope of work of pharmacists includes supply management; dispensing and distributing medication; promoting adherence; identifying and preventing potential medication-related issues; and monitoring and reporting adverse events. In some settings, programmes have implemented alternative models of pharmacy services that shift selected tasks from pharmacy to non-pharmacy personnel. Such alternative models could potentially increase the number of health workers involved in ART distribution, adherence counseling and patient education; free more time for pharmacy personnel; support integration of ART in primary care settings; minimise the number of facility visits for ART collection; and reduce pharmacy queue waiting times for patients[9].

However, the specifics of shifting ART related tasks from pharmacy to non-pharmacy personnel have not yet been addressed in a systematic review. We therefore plan to synthesise the evidence for task shifting in pharmacy services, where non-pharmacy personnel undertake ART dispensing and distribution and medication adherence counselling. For this systematic review, pharmacy personnel will include both pharmacists and pharmacy technicians. Pharmacy technicians constitute an important part of the pharmacy workforce in low and middle-income countries. A survey of 26 low and middle-income countries in 2011 revealed that pharmacy technicians constitute 10% (Nigeria) to 70% (Pakistan) of the pharmacy workforce[10].

How the intervention might work

Within the last decade, several high HIV burden countries adopted task shifting strategies where nurses and non-physician clinicians initiate and maintain ART[11]. Though this has irrefutably expanded access to ART, it is also increasingly essential that the long facility waiting time and frequent facility visits to collect ART are addressed to alleviate the burden of care, both for patients and healthcare providers[12,13].

Recent studies in Uganda, Kenya and Mozambique have shown positive outcomes when non-health professionals (lay people) delivered ART at the community level[14]. In Mozambique the use of PLHIV for distributing ART, monitoring adherence, reporting outcomes and referring sick patients to health facilities yielded a retention rate of 97.5% among stable patients on ART[14]. In a cluster randomized trial in Uganda, the use of trained community health workers produced comparable results with the facility-based ART programme in terms of patient retention, viral load suppression and mortality rate[15]. Similar findings were also obtained in Kenya and Uganda when lay providers were engaged in ART delivery[15,16].

Task shifting has therefore been seen as an achievable solution to the critical human resource shortages for scale up of ART[17]. While it is imperative to increase the rate of recruitment and training of health workers as well as improve working conditions to reduce attrition and emigration, the HIV pandemic requires a more urgent measure to address the critical skills shortage[18]. Such measures may include shifting selected tasks (including dispensing and distributing ART and adherence counseling) from pharmacy to non-pharmacy personnel. The task shifting could free time for pharmacy personnel to focus on more technical functions such as supply management and pharmacovigilance.

Why this review is important

Previous systematic reviews of task shifting for increasing ART access focused on clinical services where nurses and non-clinician physicians provide care[11]. Dependence on and shortages of pharmacists are also key constraints to ART expansion, but the specifics of task shifting for ART dispensing or distribution from pharmacy to non-pharmacy personnel have not been reviewed systematically. We will systematically review the scientific literature and assess the efficacy and safety of task shifting models that use non-pharmacy personnel in dispensing or distributing ART and assessing adherence to treatment of HIV infection.

Objective

The aim of this review is to evaluate the efficacy and safety of shifting dispensing and distribution of ART as well as assessment of adherence from pharmacy to non-pharmacy personnel.

Methods

This review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42015017034.

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and non-randomised controlled trials (non-RCTs), irrespective of whether allocation to interventions occurred at the individual or cluster level.

Types of participants

Participants will be PLHIV receiving ART.

Types of interventions

We will include studies that evaluate shifting of selected tasks from pharmacy personnel to non-pharmacy personnel. The selected tasks include dispensing and distribution of ART and adherence assessment. Pharmacy personnel will include both

pharmacists and pharmacy technicians. Non-pharmacy personnel may include (but are not limited to) nurses, non-physician clinicians, and lay providers such as patient peer groups, community volunteers, PLHIV, and community health committees.

Types of outcome measures

Primary outcomes

The primary outcome for this review is risk of death

Secondary outcomes

Our secondary outcome measures include:

- Virological suppression
- Number of all-cause sick visits made to the health facility, including adverse events
- Loss to follow-up
- Adherence to ART (as measured within the study e.g. pill counts, recall methods, digital methods)
- Acceptability to pharmacy personnel, non-pharmacy personnel, and patients
- Harm, including rates of errors.

Search methods for identification of studies

We will perform a comprehensive and exhaustive search of electronic databases and conference proceedings in an attempt to identify all relevant studies available by the search date, regardless of language of publication or publication status (published, unpublished, in press and in progress).

Databases of peer-reviewed literature

We will search the following electronic databases, in the period from 1 January 1996 to the search date:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Excerpta Medica Database (EMBASE)
- PubMed
- ISI Web of Science (Science Citation index)
- WHO Global Health Library, which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO).

Along with appropriate Medical Subject Heading (MeSH) terms and relevant keywords, we will use the Cochrane Highly Sensitive Search Strategy for identifying reports of randomized controlled trials in MEDLINE[19], and the Cochrane validated strategies for identifying references relevant to HIV infection and AIDS. To identify other study designs, the RCT string will be omitted. The search strategy will be iterative in that references of included studies will be searched for additional references. See Table 1 for our provisional search strategy for electronic databases.

Conference databases

We will search conference abstract archives on the web sites of the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), for all available abstracts presented at these conferences from 1996 through the search date.

Searching other resources

We will also search the references of relevant articles as well as WHO International Clinical Trials Registry Platform (ICTRP) and Clinicaltrials.gov. We will contact relevant experts or organisations who may be aware of additional studies in this field.

Table 1: Proposed Search strategy for electronic databases

PubMed	
ID	Search terms
#1	(task*[tiab] OR task-shifting[tiab] OR referr*[tiab] OR referral and consultation[mh] OR role*[tiab]) AND (health personnel[mh] OR doctor[tiab] OR doctors[tiab] OR clinician[tiab] OR clinicians[tiab] OR physician[tiab] OR physicians[tiab] OR "healthcare provider"[tiab] OR "healthcare providers"[tiab] OR "health care provider"[tiab] OR "health care providers"[tiab] OR pharmac*[tiab] OR apothecar*[tiab] OR chemist*[tiab] OR dispensar*[tiab])
#2	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[MeSH] OR random allocation[MeSH] OR double-blind method[MeSH] OR single-blind method[MeSH] OR clinical trial[pt] OR clinical trials[MeSH] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp] OR prospective studies[MeSH] OR control*[tw] OR volunteer*[tw]) OR observational[tw] OR non-random*[tw] OR nonrandom*[tw] OR before after study[tw] OR time series[tw] OR cohort*[tw] OR cross-section*[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals[MeSH] NOT human[MeSH])
#3	(HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or "sexually transmitted diseases, viral"[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]
#4	(HAART[tiab] OR ART[tiab] OR cART[tiab] OR antiretroviral[tiab] OR

	anti-retroviral[tiab] OR anti-viral[tiab] OR antiviral[tiab] OR "Antiretroviral Therapy, Highly Active"[Mesh])
#5	#1 AND #2 AND #3 AND #4
Scopus	
	(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TITLE-ABS-KEY (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TITLE-ABS-KEY (ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TITLE-ABS-KEY (RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")
Web of Science	
	(TS=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TS=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TS=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR CART OR HAART) AND TS=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS")) **OR** (TI=(HIV OR HIV/AIDS OR AIDS OR "HUMAN IMMUNODEFICIENCY" OR "ACQUIRED IMMUNODEFICIENCY") AND TI=(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) AND TI=(ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR cART OR HAART) AND TI=(RANDOM* OR RANDOMIZED OR RANDOMISED OR TRIAL OR COHORT* OR GROUP* OR COMPAR* OR OBSERVATIONAL OR PROSPECTIVE* OR RETROSPECTIVE* OR "SYSTEMATIC REVIEW" OR "META-ANALYSIS"))
CENTRAL	
	HIV* OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME in Title, Abstract, Keywords and (TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*))) in Title, Abstract, Keywords and ANTIRETROVIRAL OR ANTI-RETROVIRAL OR ART OR

	cART OR HAART in Title, Abstract, Keywords
WHO Global Health Library	
	(TASK-SHIFTING OR TASKSHIFTING OR (TASK* AND SHIFT*) OR TASK* OR (REFERR* AND (NURSE* OR PHARMAC*)) AND (HIV* OR human immunodeficiency) AND (antiretroviral OR anti-retroviral))) OR (HIV AND task-shifting) OR (HIV* AND task* AND shift*)

Data collection and analysis

We will base the methodology for data collection and analysis on the guidance provided in the Cochrane Handbook of Systematic Reviews of Interventions[19].

Selection of studies for inclusion

Two authors will read and assess the abstracts of identified publications for potentially eligible studies. We will obtain full text articles for all abstracts judged by at least one of the two authors, to be potentially eligible. Two authors will independently inspect these potentially eligible publications to establish the relevance of the article to the review according to the pre-specified criteria regarding study designs, participants, interventions, and outcome measures.

Data extraction and management

Two authors will independently extract data into a pre-piloted data extraction form. The following characteristics will be extracted from each included study:

Study details: Complete citations of publications associated with the study, start and end dates, location, study design characteristics, type of facility involved, investigators, funding sources, recruitment, method of randomisation, sequence generation, method of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, length of follow up, losses to follow up, withdrawals or drop-outs and other relevant details.

Details of the intervention: training of the cadre of health worker that was dispensing or distributing ART, what training or other support or supervision they received and other relevant details.

Details of participants: Trial inclusion and exclusion criteria, numbers of participants entering the trial, sex, clinical staging, CD4 count and other pertinent details.

Outcome details: Definitions of outcomes, details of how outcomes were assessed, numerators and denominators associated with each outcome, completeness of outcome data, effect estimates reported, and other relevant outcome information.

Assessment of risk of bias in included studies

We will assess the risk of bias in RCTs using the Cochrane risk of bias assessment tool for randomised studies[19]. For non-RCT studies, we will use the Cochrane risk of bias assessment tool for non-randomized studies of interventions (ACROBAT-NRSI)[20].

We will resolve any disagreements between the authors conducting duplicate independent screening of search outputs, assessments of study eligibility, extraction of data, and risk of bias assessment by discussion and consensus. Should this fail to resolve the differences, a third author will arbitrate.

Measures of effect

We will calculate and report risk ratios for dichotomous and time-to-event data and mean differences for continuous data with their 95% confidence intervals.

Unit of analysis issues

The unit of analysis will be the individual study participant. Cluster-randomised trials will be included in meta-analyses only after adjustments are made for design effect. Design effects for cluster-randomised studies will be corrected by using standard procedures, using the formula: design effect = 1 + (m - 1)r, where m is the average cluster size and r is the intra-cluster correlation coefficient.

Dealing with missing data

We will contact study authors if it is necessary to obtain data missing from published reports.

Assessment of heterogeneity

We will examine statistical heterogeneity between study results using the chi-squared (χ^2) test of homogeneity, with a significance α-level of 0.1. In addition, we will use the I^2 statistic to measure the amount of heterogeneity among the trials in each analysis. If we identify significant heterogeneity (that is, $P<0.1$), we will explore it by pre-specified subgroup analysis. If heterogeneity persists, we will perform sensitivity analyses, report results separately and propose reasons for the observed heterogeneity.

Assessment of reporting biases

If any meta-analysis in our review includes 10 or more studies, we will assess the potential for publication bias using a funnel plot[21]. We will attempt to minimise the potential for publication bias through a comprehensive search of published and unpublished literature.

Data synthesis

We will conduct meta-analysis, if appropriate, using the Cochrane Review Manager software[22]. If we find no significant statistical heterogeneity of effects, we will use the fixed effect method of meta-analysis. Otherwise, we will use the random effects model.

Subgroup analysis

In pooled results with significant statistical heterogeneity, we will explore the cause of the heterogeneity through subgroup analyses; with subgroups defined by type of intervention (e.g. cadre of health provider), comparison group, and region of study (e.g. sub-Saharan Africa, Southeast Asia etc.).

Sensitivity analysis

We will conduct a sensitivity analysis to investigate the effect of excluding studies with high risk of bias; with a focus on bias introduced by inadequate allocation concealment, inadequate blinding of outcome assessment, and substantial losses to follow up.

Certainty of evidence

We will assess the certainty (or quality) of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[23], which defines the certainty of evidence for each outcome as "the extent of our confidence that the estimates of effect are correct" [19]. The quality rating across studies has four levels: high, moderate, low or very low. Randomised trials are considered to be of high quality but can be downgraded for any of five reasons: risk of bias, indirectness of evidence, unexplained heterogeneity of effects, imprecision of effect estimates, and high probability of publication bias. Similarly, observational studies are considered to be of low quality, but can be upgraded for any of three reasons. The quality level of a body of evidence can be increased if there is a large magnitude of effect, if all plausible confounding would reduce a demonstrated effect, and if there is a dose-response gradient.

Reporting of this review

The findings of this review will be presented in a number of ways. The study selection process will be summarised using a flow diagram; and if we identify 10 or more eligible studies, we will assess publication bias using funnel plots. Where appropriate, we will use risk of bias graphs, forest plots, and GRADE summary of findings tables. The non-quantitative outcomes will be reported descriptively. We will provide tables of both included and excluded studies. We have prepared this protocol as recommended by the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) guidelines[24] and will report the findings of the review as recommended by the PRISMA statement[25].

Ethics and dissemination

Since systematic reviews do not directly involve human participants, they do not require ethical clearance[26]. We will provide the findings of this review to the World Health Organisation, with the hope that they may guide policy recommendations from this normative agency regarding the shifting of ART dispensing or distribution from pharmacy to non-pharmacy personnel. Although the majority of national programmes in low and middle-income countries have adopted task shifting in ART care at

different levels, there has been no global policy to guide the practice for task shifting from pharmacy to non-pharmacy personnel. We will also publish the findings of the systematic review in a peer-reviewed journal.

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Contributors

Nyanyiwe M. Mbeye led the development of the protocol, wrote the first draft, coordinated and integrated comments from co-authors and approved the final version for publication. Eyerusalem Negussie, Tamara Kredo, and Charles Wiysonge conceived the study, critically revised successive drafts of the manuscript, and approved the final version for publication. Charles Wiysonge is the guarantor of the manuscript.

Competing interests

No, there are no competing interests.

Provenance and peer review

Not commissioned; externally peer reviewed.

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PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Title: The effects of shifting tasks from pharmacy to non-pharmacy personnel for providing antiretroviral therapy to people living with HIV: A systematic review protocol

Section and topic	Item No	Checklist item	Page No
Administrative information			
Title:			**1**
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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 5
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	12
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	6-7
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	7-9
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Selection process	11b	State the process that will be used for selecting studies	9

		(such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
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	9
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	9
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
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-11
	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)	10-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11