



BMJ Open Effectiveness of linkage to care and prevention interventions following HIV self-testing: a global systematic review and meta-analysis protocol

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ABSTRACT

Introduction Early identification of persons living with HIV (PLWH) is crucial to institute timely treatment to prevent HIV-related morbidity and mortality. The convenience, flexibility and confidentiality of HIV self-testing enhance the acceptability of HIV testing and early detection of PLWH. However, persons who tested positive after a self-test are more likely to present late for treatment. This review seeks to evaluate the effectiveness of interventions to improve linkage to care and prevention after self-testing.

Methods and analysis We will search PubMed, Embase, Web of Science, Cochrane Library, PsycInfo, Global Health Library, ClinicalTrials.gov and current controlled trials for all randomised and non-randomised studies published from 1 January 2010 to 31 July 2022 without language restriction. Two review authors will independently screen and select articles (based on the eligibility criteria for this review), extract data and assess the risk of bias in the included studies. Study-specific estimates will be converted to log risk ratios and weighted by the inverse of the variance of the log risk ratio before pooling into a fixed-effect model. The Cochrane's Q χ^2 test and the I^2 statistic will be used to assess and quantify heterogeneity in the included studies, respectively. The Egger's test and funnel plots will be used to assess publication bias. Sensitivity analysis will be conducted using leave-one-out analysis to assess the impact of outliers on the overall summary intervention effect.

Ethics and dissemination No ethical clearance is needed for the current study as it will be based on already published articles. We will publish the findings of this study in international peer-reviewed journals and present them at conferences.

BACKGROUND

The HIV pandemic is still a significant public health concern.¹ In 2019, approximately 38 million people were living with the virus worldwide, 70% (24.7 million) of whom resided in sub-Saharan Africa (SSA).² Globally, 20% of people living with HIV (PLWH) are unaware of their status.³ HIV self-testing is a strategy where people can take an HIV test and ascertain the results on their own, usually

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will permit a systematic assessment of interventions to improve linkage to HIV care and prevention interventions among HIV self-testers.
- ⇒ Combining studies in a meta-analysis increases the power of our study, preventing chance findings and type II error.
- ⇒ We anticipate heterogeneity in study design and participants' characteristics in respective trials as a limitation to the study.

in their homes or other private locations.⁴ HIV self-testing is essential in reaching PLWH with limited access to conventional health facility-based testing services and increases coverage of essential HIV services.^{5,6} This is particularly important for hard-to-reach groups like men, men who have sex with men (MSM) and injecting drug users.⁷⁻⁹ The convenience, flexibility, privacy and confidentiality offered by self-testing facilitates its acceptability among HIV-infected individuals.^{7,8} Studies have documented a higher preference for, and effectiveness of, self-testing among the general population in SSA.^{7,9-11}

Although antiretroviral therapy (ART) coverage in SSA has increased significantly over the past two decades, about 10.3 million PLWH remain untreated with ART.¹² Even those who seek treatment usually do it too late.¹³⁻¹⁵ Linking self-testers to care and prevention are vital in the fight against HIV.¹¹ Indeed, the linkage to care and prevention after self-testing for HIV constitutes an essential strategy of achieving the global Sustainable Development Goal (SDG) 3.3 target of ending the HIV/AIDS epidemic by the year 2030.¹⁶ In the pursuit of achieving the SDG target, governments have implemented various interventions in SSA to address the delay in linkage to care. These include

non-cash financial incentives and transport reimbursement, health system interventions such as integration of HIV services into routine care, patient convenience and accessibility comprising home-based initiation of ART after HIV self-test, and behavioural interventions and peer support (ie, assisted partner services, care facilitation, mobile phone appointment reminders and health education).^{11 17–26}

Evidence from a recent systematic review revealed that men, who are less likely to go in for an HIV test than women, are more likely to accept test for HIV using a self-test approach than traditional clinic-based approaches.²⁷ Key groups such as female sex workers and MSM who bear a high burden of HIV infection and face stigma in accessing healthcare services can benefit from HIV self-testing services.^{28 29}

With increasing and almost conclusive evidence regarding the potential of self-testing approaches to increase the timely awareness of HIV status, the effectiveness of interventions to improve linkage self-testers to care remain systematically undocumented. This systematic review and meta-analysis aim to evaluate the effectiveness of interventions to improve linkage to HIV care and prevention after self-testing. The findings could provide detailed scientific evidence on strategies needed to improve policy and practice regarding effective linkage of self-testing and comprehensive HIV care.

Objective

This study aimed to evaluate the effectiveness of interventions to improve linkage to HIV care and prevention after self-testing compared with standard of care.

METHODS

Criteria for considering studies into the review

Inclusion criteria

1. Interventional studies (randomised and non-randomised controlled trials) that evaluated the effectiveness of interventions to improve linkage to HIV care or prevention after self-testing for HIV.
2. Age limit: We will consider studies done among participants of at least 15 years of age. We chose 15 years as threshold because most studies on HIV include individuals within the sexual reproductive age group (ie, 15–49 years).
3. The primary outcomes will be percentage of persons linked to HIV care after testing positive, and the percentage of persons that receive HIV prevention services (most especially, pre-exposure prophylaxis (PrEP)) after testing negative.
4. For duplicate studies, only those with the most recent findings or larger sample size will be considered.
5. Studies published from 1 January 2010 to 31 July 2022.

Exclusion criteria

1. Editorials, commentaries, review articles and case series.

2. Studies with insufficient information to summarise data on effectiveness of interventions to improve linkage to HIV care after self-testing.

Information sources

Search strategy for identifying relevant studies

We will search PubMed, Embase, Web of Science, Cochrane Library, PsycInfo, Global Health Library, ClinicalTrials.gov and current controlled trials for relevant studies published from 1 January 2010 to 31 July 2022. We will use key text and medical subject headings that capture keywords like HIV self-testing, HIV home testing, and linkage or enrolment to HIV care (online supplemental table S1–S8).

We will supplement database searches by searching ResearchGate and Google Scholar for grey literature. The reference list of any available relevant review or eligible full-text articles will be perused to identify studies missed during our search.

Study records

Data management

Citations retrieved from database searches will be imported into EndNote V.X9 to remove duplicate citations. We will then export the unduplicated citations (containing the article title and abstract) to Rayyan QCRI for screening.³⁰ Data from eligible full-text articles will be extracted using a secure predesigned Google Form. Using a web-based electronic questionnaire facilitates monitoring of the data extraction process in real time, thereby improving the quality of the data extraction process.

Study screening

Two review authors will independently screen citations retrieved from database searches based on title and abstract. The full-text articles of potentially eligible citations will be downloaded, and two authors will then assess them for final inclusion in the review (based on the eligibility criteria for this review). Disagreements between review authors during the screening stage will be resolved through discussions. A third author will only be called on for arbitration if disagreements between authors persist.

Data item and extraction

We will extract data on the surname of the first author, article publication year, country where the study was conducted, WHO region of the country of study, female proportion, mean or median age in years, trial design, characteristics of study participants, description of intervention and comparison, and sample size. To assess effectiveness of interventions to linkage to HIV care among self-testers, we will extract data on the number of persons tested HIV positive following (1) HIV self-testing and were linked to HIV care; (2) HIV self-testing but were not linked to HIV care; (3) a controlled testing approach and were linked to HIV care; and (4) a controlled testing approach and were not linked to HIV care.

To assess effectiveness of interventions to linkage to PrEP, we will extract data on the number of persons

who tested HIV negative following (1) HIV self-testing and were offered PrEP; (2) HIV self-testing but were not offered PrEP; (3) a controlled testing approach and were offered PrEP; and (4) a controlled testing approach and were not offered PrEP. Where information on the stratum-specific frequency is not reported, we will extract information on the effect size (eg, OR or risk ratio) and their corresponding SEs (or CIs) comparing the primary outcomes in the intervention and control groups. Where possible, data from multinational studies will be disaggregated and presented according to the country in which the study was conducted.

Assessment of methodological quality and risk of bias

The updated Cochrane's risk of bias assessment tool for randomised controlled trial, RoB 2.0, will be used to assess the risk of bias of the included study.³¹ This tool was selected because it is more robust, easy to understand, and the recent version was developed to account for potential issues with lack of blinding in these trials. The tool evaluates five major compartments of the original study that includes bias due to (1) randomisation, (2) deviation from the intended intervention, (3) missing outcome data, (4) measurement of the outcome and (5) selection of the reported results. Each major compartment is assessed using questions with five possible responses: not applicable, yes, probably yes, no, probably no and no information. An algorithm that comes with the toolset will be used to guide the author's decision in rating each major section as either low risk of bias, some concerns on the methods or high risk of bias. A study will be qualified as having a low risk of bias if all the five major compartments were rated as having low risk of bias. If the study was rated to have some concerns in one or more domain, with no domain rated as high risk, the study will be rated as having 'some concerns'. A study will be judged to be at high risk of bias if (1) at least one domain is assessed to be at high risk of bias or (2) there are multiple domains with some concerns such that it significantly reduces the confidence in the results reported by the authors.

Data synthesis and analysis

The *'metafor'* package of the R programming software will be used for data analysis and visualisation. All study-specific effect sizes will be converted to log risk ratios (RRs), weighted using the inverse of the variance of the logRR before pooling using a fixed-effect meta-analysis model.

The Cochrane's Q χ^2 test and the I^2 statistic will be used to assess and quantify heterogeneity in the included studies, respectively.³² I^2 values of 25%, 50% and 75% will constitute low, moderate and substantial degree of heterogeneity, respectively.³³ Depending on the number of studies available for meta-analysis, substantial heterogeneity between studies will be investigated through meta-regression or subgroup analysis using the following variables: trial design, female proportion, WHO region and median age of study population. Egger's test and the

symmetry of funnel plots will be used to assess for publication bias.³⁴ A p value <0.1 on Egger's test will be considered statistically significant.

We will conduct a leave-one-out sensitivity analysis to identify the effect of outliers on the overall summary estimate.

Presentation and reporting of results

This review will be published following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. The process of study selection will be displayed with the help of a flow chart. A summary of the included trials, average treatment effect and risk of bias will be presented using tables, forest plots and funnel plots, respectively.

Protocol amendment

We do not intend to modify the current protocol. However, any modification of the protocol will be clearly described in the final report.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Ethics and dissemination

No ethical clearance is needed for the current study as it will be based on already published articles. We will publish the findings of this study in international peer-reviewed journals and present them in conferences.

DISCUSSION

HIV self-testing is a promising approach, most especially in putting hard to reach populations on treatment on time. This is fundamental in breaking the transmission chain and allowing persons to live longer. The gains expected from HIV self-testing will not be achieved if these persons fail either to link to care or to prevention. Understanding the effectiveness of these interventions, and the reported barriers and facilitators to linkage to care and prevention, will allow for health policies that will improve testing and linkage to care rates. The focus in the recent literature has been on linking persons who self-test positive to care. This review has an added value, as it seeks to identify interventions that link persons who test negative to prevention interventions, and most especially PrEP and other behavioural change interventions.

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Contributors LEB conceived the study. LEB and VNA designed the study and drafted the protocol. HA, RKD and PM critically revised the protocol for methodological and intellectual content. All authors read and approved the final version of the manuscript prior to submission. VNA is the guarantor of the review.

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REFERENCES

- Ghoma Linguissi LS, Lucaccioni V, Bates M, *et al*. Achieving sustainable development goals for HIV/AIDS in the republic of the congo - progress, obstacles and challenges in HIV/AIDS health services. *Int J Infect Dis* 2018;77:107–12.
- World Health Organization [WHO]. Estimated number of people (all ages) living with HIV. Geneva; 2021. [https://www.who.int/data/gho/data/indicators/indicator-details/GHO/estimated-number-of-people-\(all-ages\)-living-with-hiv](https://www.who.int/data/gho/data/indicators/indicator-details/GHO/estimated-number-of-people-(all-ages)-living-with-hiv) [Accessed 15 Apr 2021].
- UNAIDS. Seizing the moment - tackling entrenched inequalities to end epidemics. Geneva; 2020. <https://www.unaids.org/en/resources/documents/2020/global-aids-report> [Accessed 15 Apr 2021].
- Centres for Disease Control and Prevention (CDC). Hiv: Self-testing, 2021. Available: <https://www.cdc.gov/hiv/testing/selftesting.html#:~:text=Related%20Pages,otherwise%20get%20an%20HIV%20test>
- Tang S, Tang W, Meyers K, *et al*. Hiv epidemiology and responses among men who have sex with men and transgender individuals in China: a scoping review. *BMC Infect Dis* 2016;16:1–8.
- World Health Organization. Report on the first International Symposium on self-testing for HIV: the legal, ethical, gender, human rights and public health implications of HIV self-testing scale-up. Geneva, Switzerland; 2013: 8–9.
- Tonen-Wolyec S, Mbopi-Kéou F-X, Batina-Agasa S, *et al*. Acceptability of HIV self-testing in African students: a cross-sectional survey in the Democratic Republic of Congo. *Pan Afr Med J* 2019;33:83.
- Estem KS, Catania J, Klausner JD. Hiv self-testing: a review of current implementation and fidelity. *Curr HIV/AIDS Rep* 2016;13:107–15.
- Mokgatle MM, Madiba S. High acceptability of HIV self-testing among technical vocational education and training college students in Gauteng and North West province: what are the implications for the scale up in South Africa? *PLoS One* 2017;12:e0169765.
- Dzinamarira T, Muvunyi CM, Kamanzi C, *et al*. Hiv self-testing in Rwanda: awareness and acceptability among male clinic attendees in Kigali, Rwanda: a cross-sectional survey. *Heliyon* 2020;6:e03515.
- Koduah Owusu K, Adu-Gyamfi R, Ahmed Z. Strategies to improve linkage to HIV care in urban areas of sub-Saharan Africa: a systematic review. *Hiv Aids* 2019;11:321.
- Nash D, Yotebieng M, Sohn AH. Treating all people living with HIV in sub-Saharan Africa: a new era calling for new approaches. *J Virus Erad* 2018;4:1–4.
- World Health Organisation. Hiv treatment reaching 6.6 million people, but majority still in need; 2011. http://www.who.int/mediacentre/news/releases/2011/hivtreatment_20110603/en/index.html [Accessed 16 Apr 2021].
- Fairall LR, Bachmann MO, Louwagie GMC, *et al*. Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Arch Intern Med* 2008;168:86–93.
- May M, Boule A, Phiri S, *et al*. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. *Lancet* 2010;376:449–57.
- United Nations. *Transforming our world: the 2030 agenda for sustainable development*. New York, 2015.
- McNairy ML, Lamb MR, Gachuhi AB, *et al*. Effectiveness of a combination strategy for linkage and retention in adult HIV care in Swaziland: the Link4Health cluster randomized trial. *PLoS Med* 2017;14:e1002420.
- Greene E, Pack A, Stanton J, *et al*. "It makes you feel like someone cares" acceptability of a financial incentive intervention for HIV viral suppression in the HPTN 065 (TLC-Plus) study. *PLoS One* 2017;12:e0170686.
- Bekker LG, Montaner J, Ramos C. IAPAC guidelines for optimizing the HIV care continuum for adults and adolescents. *J Int Assoc Provid AIDS Care* 2015;14 Suppl 1:S3–34.
- Govindasamy D, Meghij J, Kebede Negussu E, *et al*. Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings--a systematic review. *J Int AIDS Soc* 2014;17:19032.
- Fox MP, Rosen S. Retention of adult patients on antiretroviral therapy in low- and middle-income countries: systematic review and meta-analysis 2008–2013. *J Acquir Immune Defic Syndr* 2015;69:98–108.
- Mugglin C, Estill J, Wandeler G, *et al*. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. *Trop Med Int Health* 2012;17:1509–20.
- Chanda MM, Ortblad KF, Mwale M, *et al*. Hiv self-testing among female sex workers in Zambia: a cluster randomized controlled trial. *PLoS Med* 2017;14:e1002442.
- Croxford S, Yin Z, Burns F, *et al*. Linkage to HIV care following diagnosis in the who European region: a systematic review and meta-analysis, 2006–2017. *PLoS One* 2018;13:e0192403.
- Johnson AS, Johnson SD, Hu S. *Monitoring selected national HIV prevention and care objectives by using HIV surveillance data: United States and 6 dependent areas*, 2017.
- Hlongwa M, Mashamba-Thompson T, Makhunga S, *et al*. Men's perspectives on HIV self-testing in sub-Saharan Africa: a systematic review and meta-synthesis. *BMC Public Health* 2020;20:66.
- Harichund C, Moshabela M, Kunene P, *et al*. Acceptability of HIV self-testing among men and women in KwaZulu-Natal, South Africa. *AIDS Care* 2019;31:186–92.
- Widyanthini DN, Januraga PP, Wisaksana R, *et al*. Hiv self-testing for men who have sex with men: an implementation trial in Indonesia. *AIDS Care* 2022;34:1–8.
- Shava E, Manyake K, Mdluli C, *et al*. Acceptability of oral HIV self-testing among female sex workers in Gaborone, Botswana. *PLoS One* 2020;15:e0236052.
- Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile APP for systematic reviews. *Syst Rev* 2016;5:210.
- cochrane. Available: <https://methods.cochrane.org/risk-bias-2>
- Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101–29.
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.