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Male partner unknown HIV status as a risk factor for HIV incidence and clinical outcomes in prevention of mother-to-child transmission of HIV programmes in 21 WHO priority countries: a systematic review protocol

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ABSTRACT

Introduction Research has shown an association between increased disclosure of HIV status by pregnant and breastfeeding women and improved clinical health and that of their infant. Increasing awareness about their male partner's HIV status will no doubt lead to even better outcomes at the population level. Male partner involvement is important for improving outcomes of prevention of mother-to-child transmission of HIV (MTCT) as it improves social support and commitment from both parents of the baby to ensure sustained good health. Although lack of knowledge of the HIV status of a male partner is of great concern, limited research has been done to determine whether it remains one of the barriers to reaching the proposed goals of eliminating MTCT in pregnant or postpartum women. Our aim is to determine if lack of knowledge of a male partner's HIV status is a significant risk factor for HIV incidence and poor HIV clinical outcomes among pregnant women and postpartum women and their infants.

Methods and analysis A systematic review and meta-analysis of experimental and observational studies will be conducted. The review will focus on knowledge of male partner's HIV status in the 21 priority countries most affected by HIV in Africa. We will search electronic databases such as PubMed/Medline, Scopus, Web of Science and Cochrane library, Science Direct, CINAHL, LILACS and SciELO databases from January 2011 to December 2021. We will also search the Pan African and WHO clinical trial registries and conference archives. We will conduct a quality assessment of eligible studies and evaluate the heterogeneity of the pooled studies using the I^2 statistic. The statistical analysis will be performed using STATA statistical software V.16.

Ethics and dissemination The study will use publicly available data and ethics exemption has been obtained from Human Research Ethics Committees, Faculty of Medicine & Health Sciences, Stellenbosch University. The protocol was registered on Prospective Register of Systematic Reviews, registration number CRD42021247686, in May 2021. Findings of this systematic review will be disseminated in peer-review journals including various media platforms, that is, webinars, symposia, conferences or congresses.

PROSPERO registration number Registration number CRD42021247686.

Strengths and limitations of this study

- This study protocol outlines a path that will minimise data duplication and provides clear and transparent methods used.
- This study will provide quality evidence through a rigorous methodological process which follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines including meta-analysis and quality assessment of studies using the Risk of Bias for Non-Randomised Studies of Interventions and Quality in Prognostic Studies Tools.
- This systematic review will arguably be the first to review the role of male partner unknown HIV status on HIV incidence and clinical outcomes in prevention of mother-to-child transmission of HIV (PMTCT) programmes in 21 WHO priority countries.
- There is potential limitation arising from publication bias due to inclusion of English only studies and methodological inability to include qualitative studies.

INTRODUCTION

Burden of HIV in mothers and children

For almost two decades, it has been a top priority to eliminate HIV incidence among pregnant and postpartum women and their children.[1–3] In 2010, the WHO recommended provision of lifelong antiretroviral therapy (ART) to pregnant women regardless of CD4 count, known as the prevention of

mother-to-child transmission of HIV (PMTCT) Option B+ policy.[4] Concurrently, 21 countries which historically had limited access to CD4 testing services and partner testing, high-fertility rates, prolonged breastfeeding periods and a high generalised HIV epidemic were prioritised for HIV elimination targets. These countries also accounted for 90% of the world's HIV positive cases in pregnant women and in a 2020 report most of these countries accounted for more than two-thirds up to one-fifth of the newly infected children.[4 5] Despite lifelong ART under the Option B+ regimen, the PMTCT programmes have been slower than anticipated in eliminating HIV incidence in mothers and children. A 2020 report has shown that even with increased ART coverage among pregnant and breastfeeding women in the 21 priority countries, mother-to-child transmission of HIV (MTCT) ranged from 2% (in Botswana) to 28% in the Democratic Republic of Congo.[5] Several factors are responsible for the delay in meeting the HIV elimination targets. Uptake of ART and timing of initiation are very important in the PMTCT cascade as they affect the effectiveness of the programme[6 7] and delayed initiation is likely to increase maternal viral load thus increasing risk for MTCT.[8] Additionally, unplanned pregnancies, multiple pregnancies and low education attainment have also been reported as risk factors for MTCT as well as poor ART outcomes.[9–11] Younger and adolescent women are also more likely to vertically transmit HIV to their infants because of their increased likelihood of poor ART outcomes.[12 13] Fear of disclosure is another risk factor as it may lead to intimate partner violence and reduced partner support for PMTCT or ART initiation.[14]

Disclosure of HIV status is a complex risk factor in PMTCT programmes

Disclosure of HIV status is a complex risk factor for not achieving PMTCT targets, given copresence of other-related risk factors such as women not knowing their own HIV status or their male partner's HIV status as well as low partner testing.[9 13 15 16] Since the end of 2014, pregnant women HIV disclosure rates have been increasing. Results from a meta-analysis found that more than 67% of pregnant women in sub-Saharan Africa had disclosed their HIV status.[17] Increased disclosure rates were also evident in subsequent studies conducted after 2015, with disclosure rates of 80%, 85%, 94.9% and 99% in Kenya, Nigeria, Malawi and Uganda, respectively[6 18–21] and disclosure to male partners was more evident than disclosure to family members.[6 17 19] According to Bucagu *et al*,[21] HIV status disclosure is more frequent in women than in men and disclosure is generally higher in steady partners than in casual partners. HIV positive status non-disclosure of both male partners and pregnant or postpartum women was a strong predictor of suboptimal ART adherence and MTCT.[13] A systematic review on factors that influence maternal and infant ART adherence found that HIV status non-disclosure in HIV positive pregnant and postpartum women to their male partners or family was one of the factors resulting in suboptimal ART adherence.[11] Non-adherence to ART and poor ART outcomes were significantly associated with increased proportions of non-disclosure among pregnant and postpartum women.[6 21 22] Non-disclosure to either male partners, family or coworkers made it difficult for women to comply with attendance or participation in PMTCT programmes resulting in greater rates of loss to follow-up and poorer ART outcomes.[21 23] This shows that disclosure, especially to male partners, is important for improved ART outcomes thus prevention of HIV mortality and reducing HIV incidence in infants as well as keeping their mothers healthy but it remains unclear whether knowing their male partner's HIV status has also improved over the years.

Research on knowing the male partner's HIV status

The uptake of HIV Testing Services (HTS) among men is generally low, and research has shown that male partners of pregnant or postpartum women have no concerns when it comes to knowing their HIV status or with HIV prevention.[24] A 2018 study conducted in the Delanta District in Ethiopia found that men also had fears when it comes to testing for HIV, only 57% men were involved in HTS.[25] In a facility-based study conducted between August 2011 and March 2012 across all nine provinces in South Africa, the prevalence of not knowing a male partner's HIV status among pregnant and breastfeeding women was reported to be as high as 34%.[26] Given evidence of an association between increased disclosure of pregnant and breastfeeding women's HIV status and improvement in their HIV clinical health and that of their infants,[21] increasing awareness about their male partner's HIV status will no doubt lead to even better outcomes at the population level. Figure 1 shows a summary of reported and potential (red arrows) role of male-partner HIV disclosure within the PMTCT causal pathways. Although not knowing a male partner's HIV status is a potential concern, limited research has been done to determine whether it remains one of the barriers to reaching the proposed goals to eliminate MTCT and HIV in pregnant or postpartum women. This systematic review and meta-analysis aim to determine whether not knowing a male partner's HIV status is a significant risk factor for HIV incidence and poor HIV clinical outcomes among pregnant and postpartum women and their infants in the 21 WHO priority countries for eliminating MTCT.

METHODS AND ANALYSIS

The protocol has been developed in accordance with the 2015 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (online supplemental file 1).[27] This systematic review is registered with the United Kingdom's National Institute of Health Research Prospective Register of Systematic Reviews registration number CRD42021247686.

Inclusion criteria

All studies that report the knowledge of the HIV status of the male partner as an exposure or predictor factor for

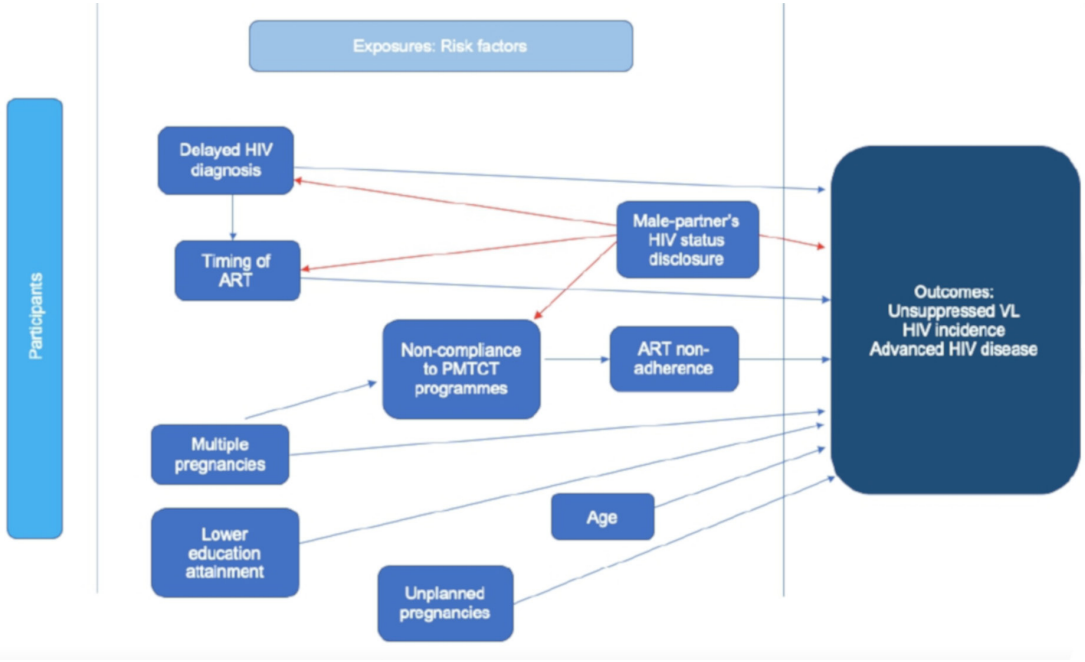

Figure 1 A summary of reported and potential role of male-partner HIV disclosure within the prevention of mother-to-child transmission of HIV (PMTCT) causal pathways. ART, antiretroviral therapy; VL, HIV viral load.

HIV incidence, viral load or CD4 count or WHO HIV clinical disease stage during pregnancy or postpartum period among women or their infants aged 0–24 months from the 21 priority countries most affected by HIV in Africa (table 1) will be reviewed. The studies should also have been conducted after the adoption of the PMTCT Option B+ regimen in these listed countries (from the year 2011). We will include English language or articles translated into the English language. Studies reporting measures of association, that is, experimental (randomised control trials and non-randomised trials) and observational studies (case-control, cohort and cross-sectional studies) will all be included.

Table 1 WHO/The Joint United Nations Programme on HIV/AIDS global priority countries and adoption of prevention of mother-to-child transmission of HIV Option B+ regimen[4]

Countries included	
Angola	Mozambique
Botswana	Namibia
Burundi	Nigeria
Cameroon	Tanzania
Chad	The Democratic Republic of the Congo
Côte d'Ivoire	South Africa
Ethiopia	Swaziland
Ghana	Uganda
Kenya	Zambia
Lesotho	Zimbabwe
Malawi	

Exclusion criteria

Publications not from the priority countries listed in table 1 or reporting outcomes from the option A or option B policies, or outcomes that are not HIV incidence, viral load, CD4 count and WHO HIV clinical disease staging will not be included. Qualitative studies will not be included.

Information sources and search strategy

A comprehensive search will be conducted in the following databases: PubMed (via Medline), the Cochrane Library, Scopus, Web of Science, Science Direct, CINAHL, LILACS and SciELO. Additional searches will be conducted from the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za/), International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform), clinicaltrials.gov as well as published conference abstracts from the International AIDS Society Conference, Conference on Retroviruses and Opportunistic Infections and the International Conference on AIDS and Sexually Transmitted Infections in Africa. Reference lists of included studies will also be reviewed to identify any eligible studies that could be added.

The systematic search will be done using various combinations of synonyms of the key search terms that define the Population and the overarching Outcome from the Participant/Exposure/Comparison/Outcome/Time-period/Setting (PECOTS) elements[28] of the research question (table 2). Search terms will include: "HIV" or "AIDS" or "MTCT" for the Outcome and "Pregnant" or "Breastfeeding" or "Postpartum women" for the Population. A pilot exercise will be conducted to identify other synonyms and search terms/phrases needed to develop

Table 2 The PECOTS framework

P—Participants	HIV positive pregnant and breastfeeding women, HIV negative pregnant and breastfeeding women, Infants born to HIV positive women
E—Exposure	Lack of knowledge of male partner's HIV status
C—Comparison	Knowledge of male partner's HIV status
O—Outcome	Unsuppressed viral load, HIV incidence, Advanced HIV disease (defined using CD4 count or WHO clinical staging)
T—Time period	Post adoption of the PMTCT Option B+ regimen in that country
S—Setting	21 WHO priority countries

PMTCT, prevention of mother-to-child transmission of HIV.

an exhaustive search strategy (see preliminary search strategy in online supplemental file 2). All studies found will be uploaded into RAYYAN—a systematic review managing software, for further processing[29] and duplicate articles will be removed.

Selection process

The selection of studies will be done in duplicate by two reviewers (TMM, NKN) and discrepancies will be resolved by discussing with a third reviewer (PN, OA). The screening and selection of the manuscripts will be done in several steps and informed by the inclusion criteria of the PECOTS.[27]

Proposed steps to guide the screening and selection process of manuscripts that will be uploaded on to the RAYYAN system are presented in figure 2 in the following order: (1) titles and abstracts will be screened for the research question's Population and Outcomes, full text articles from this step will be downloaded; articles with the following characteristics will then be selected: (2) meets the study Setting (WHO priority country) and the Population and Outcomes of the inclusion criteria; (3) publishing data from the defined Time period (during Option B+ policy); (4) meet the study design as per inclusion criteria (experimental and observational studies); and (5) have included the Exposure of interest in the data as a predictor/exposure variable.

Data extraction

Data from the selected full-text manuscripts will be extracted independently by the two reviewers (TMM, NKN) using a standardised piloted extraction form. Any discrepancies will be resolved by an agreement between the two reviewers or the third if there is no resolution (OA, PN). In cases where additional information is required such as clarifying on information, missing information or regarding relevant data that may not have been included in the manuscript, the authors will contact the corresponding author of the primary studies to access the information.[27]

The following data parameters will be extracted; author, title of the study, study setting, study design, study sample and population, year of study, measure of association or effect between the exposure of interest and HIV incidence/clinical disease.

Quality of manuscripts

Study quality and risk of bias will be assessed by evaluating the study design, data collection as well as the data analysis methods. The quality assessment will be double-checked

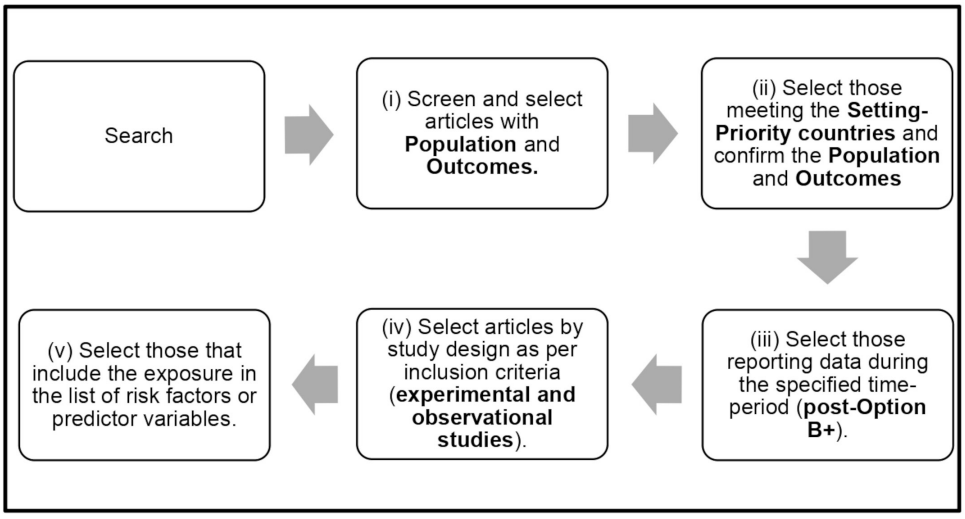

Figure 2 Flowchart showing detailed summary of the search and screening processes.

by the review team. The risk of bias of randomised studies will be assessed using the Cochrane Risk of Bias Tool.[30] The Risk of Bias for Non-Randomised Studies of Interventions Tool[31] will be used for non-randomised trials while the Quality in Prognostic Studies Tool[32] will be used for observational studies. The summary of characteristics of each study will be presented in a table format.

Synthesis of results

A meta-analysis will be performed if the selected manuscripts are homogenous in terms of methodology and outcomes. Data that is sufficiently similar will be pooled together using the inverse variance approach to accommodate crude and adjusted measures of association and effect, where possible.[27] Additionally, the meta-analysis will be presented using pooled estimates with 95% CI as well as the estimate of the between study variance.[27] The studies reporting similar measures will be grouped accordingly, that is, HRs, ORs and risk ratios (RRs). Those reporting adjusted and crude measures will also be grouped separately. Where data are available, mean difference with its SD for continuous data such as VL will be calculated while ORs or RRs will be used for categorical data. Statistical heterogeneity assessment will be done using the I^2 statistic,[33] by examining the results using the χ^2 test with p≤0.10. We will consider I^2 statistical values between 30% and 60% as moderate heterogeneity; >60% and 90% as substantial heterogeneity; and >90% and 100% as considerable heterogeneity. It is important to note that the I^2 statistic depends on the direction and magnitude of effects across several studies as well as the strength of evidence for heterogeneity.[33] A random effects model will be used. We will conduct subgroup analysis by study designs and study settings (ie, country) where substantial heterogeneity exists. To determine publication bias, a Funnel Plot and Egger's test will be used. All analyses will be performed using STATA V.16.[34]

In a case where quantitative synthesis is not possible, information will be presented in text format as well as tables to summarise and present the characteristics and findings of the studies in a narrative systematic synthesis to explore the relationship between lack of knowledge of male partner's HIV status and maternal and child health outcomes as per data from the included studies. This synthesis will be guided by the Centre for Reviews and Dissemination.[35]

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation working group methodology will be used to judge the quality of evidence for all outcomes.[36] The following domains will be used for this assessment, "risk of bias, inconsistency, indirectness, imprecision and publication bias". Given this is a prognostic type research question unlike in therapeutic studies, observational studies will be ranked with higher certainty of evidence compared with Randomized Control Trials. The higher confidence in observational studies for prognostic factor studies is due to the stricter eligibility criteria in RCTs which is likely to exclude the population of interest for the prognostic question.[36] The significance levels of evidence for the risk associated with not knowing the HIV status of a male partner will be ranked as high, moderate, low or very low.[37]

Presenting and reporting of results

We plan to display the study selection process by means of a flow diagram and give reasons for exclusion of studies. Reporting of the results will follow PRISMA guidelines.[27] We will display the search strings, risk of bias tables, forest plots and summary of study findings tables.[27]

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

The study will use publicly available data and ethics exemption has been obtained from the Human Research Ethics Committee, Faculty of Medicine & Health Sciences, Stellenbosch University. Findings of this systematic review will be disseminated in peer-review journals including various media platforms, that is, webinars, symposia, conferences or congresses.

DISCUSSION

This systematic review will provide an overview of how lack of disclosure of male partner's HIV status to pregnant and postpartum women affects progress towards eliminating HIV incidence and reducing HIV morbidity in pregnant and postpartum women and their infants. This systematic review will arguably be the first to explore the risk of male partner unknown HIV status on HIV incidence and clinical outcomes in PMTCT programmes in the 21 WHO priority countries. As a result of a clearly outlined protocol, there will be minimum duplication of data. This protocol also ensures that a clear and transparent procedure is used. Some limitations are foreseen in this study, such as the non-inclusion of qualitative studies in the meta-analysis methodology to be used, potentially low methodological quality of studies from grey literature (eg, policy reports) and low statistical power for meta-analysis where few included studies report on the same outcome. However, the study will still help to highlight knowledge gaps in the WHO priority countries about the role of knowing a male partner's HIV status in improving PMTCT programme effectiveness. There is generally scarcity in randomised and non-randomised trials assessing the impact of male involvement in MTCT of HIV programmes as well as studies specifically focused on the impact of lack of knowledge of male partner HIV status on maternal as well as child outcomes. This systematic review will therefore likely pave the way for more primary studies to explore male partner HIV status disclosure as a possible risk factor.

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Competing interests None declared.

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Patient consent for publication Not applicable.

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