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Impact of point-of-care diagnostics on maternal outcomes in HIV-infected women: systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Studies indicate substandard diagnostic care, delayed and missed diagnosis as some of the contributing factors to maternal mortality. The clinical impact of point-of-care (POC) diagnostics has been shown in the monitoring and treatment of a variety of infectious diseases, including HIV/AIDS and tuberculosis. The objective of this systematic review is to investigate the impact of POC diagnostics on maternal outcomes for HIV-infected women.

Methods: We will conduct a systematic review to evaluate the impact of POC diagnostics for improving desired healthcare outcomes for HIV-infected women. The search strategy will involve electronic databases including: Cochrane Infectious Disease Group Specialised Register; Cochrane Central Register of Control Trials, published in The Cochrane Library; PubMed; EBSCOhost and LILACS. The studies will be mapped in 2 stages: stage 1 will map studies descriptively by focus and method; stage 2 will involve additional inclusion criteria, quality assessment and data extraction undertaken by 2 reviewers in parallel. Evidence will be synthesised using relevant systematic research tools: meta-analysis and subgroup analysis will be conducted using *RevMan* and Stata 13 will be used for meta-regressions. We will follow recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Intervention Reviews.

Ethics and dissemination: We anticipate finding a large number of studies on POC diagnostic interventions on maternal outcomes in HIV-infected women, which, once summarised, will be useful to guide future diagnostic interventions. The protocol for the systematic review has been registered in PROSPERO. The study will be disseminated electronically and in print. It will also be presented to conferences related to HIV/AIDS, POC diagnostics and maternal health.

Trial registration number: PROSPERO CRD42014015439.

INTRODUCTION

Maternal mortality remains a major challenge to health systems worldwide.[1] According to the 2013 WHO and UNAIDS global estimates, women comprise 50% of people living with HIV.[2] Elimination of new HIV infections among children and substantially reducing AIDS-related maternal deaths is a major global priority that has been integrated into many countries' national strategic plans.[2 3] Studies indicate that substandard diagnostic care, and delayed and missed diagnosis, are some of the contributing factors to maternal mortality in low-income and middle-income countries.[4–6] One factor that has been associated with poor maternal and infant morbidity is the lack of male partner involvement in antenatal care and testing.[7 8]

The clinical impact of appropriately used point-of-care (POC) diagnostics has been shown in the monitoring and treatment of a variety of infectious diseases, including HIV/AIDS and tuberculosis.[9] The WHO called for new clinical diagnostic methods that are designed to function in settings with limited access to laboratory services,[10] leading to an increase in development, marketing and manufacturing of POC diagnostic instruments for use at the clinical POC.[11] A recent systematic review reports the acceptability of self-testing using POC diagnostics and its impact on improving partner testing.[12] However, the lack of evidence on post-test linkage with counselling and treatment outcomes with the use of self-testing POC diagnostic has been demonstrated.[12] From a public health perspective, it is advisable to recommend increased availability of POC testing that includes counselling to those at risk of HIV and to make testing easily accessible. However, previous research has shown that the availability of health technologies does not always guarantee improved patient-centred outcomes.[13] Moreover, little has been published in a systematic way on the

impact of HIV-related POC diagnostics on maternal outcomes for HIV-positive women. We raise the following question: What is the impact of POC diagnostics compared with conventional laboratory testing on maternal health outcomes for HIV-positive women? The research aims are as follows:

- What impact do HIV-related POC diagnostic interventions and timely receipt of test results or diagnosis have on reduction of maternal mortality?
- What impact do HIV-related POC diagnostic interventions have on prevention of maternal and child transmission?
- What impact do HIV-related POC diagnostic interventions have on successful linkage to HIV care and initiation of antiretroviral therapy (ART)?
- What is the impact of HIV-related POC diagnostic interventions on maternal and child morbidity?
- What is the impact of HIV-related POC diagnostic interventions on partner testing?

In order to address the above research questions, the following objectives will be outlined:

- To evaluate whether the introduction of HIV-related POC diagnostics into antenatal care has an impact on maternal mortality rates.
- To evaluate whether the introduction of HIV-related POC diagnostics into antenatal care has an impact on vertical (ie, mother-to-child) HIV transmission rates.
- To evaluate whether the introduction of HIV-related POC diagnostics into antenatal care has an impact on successful linkage to continuity of HIV care and start of antiretroviral treatment.
- To evaluate whether or not introduction of HIV-related diagnostics into antenatal care has an impact on maternal and child morbidity.
- To evaluate whether or not introduction of HIV-related diagnostics into antenatal care has an impact on partner testing.

METHOD

The systematic review will follow recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14] and the Cochrane Handbook for Intervention Reviews.[15] The findings of the systematic review will be disseminated through publication in a peer-reviewed journal and will be formatted according to the specific journal's publication guidelines.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Search methods for identification of studies

Stage 1: Identifying and describing studies

We will identify relevant trials that are published in English regardless of publication status (table 1).

Electronic search

Databases: We will search the following databases from 2000 to February 2014: Cochrane Infectious Disease Group Specialised Register; Cochrane Central Register of Control Trials, published in The Cochrane Library; PubMed; EBSCOhost and LILACS. In addition, we will also search the grey literature using the metaRegister of controlled trials (mRCT) and the WHO trials register using prescribed search terms. We will undertake an intensive process of reference-checking of relevant papers, not only those references cited in the papers, but also looking for those papers that cite our target papers (using citation indexing in Web of Knowledge) and the related citations facility in MEDLINE. Data abstraction will be carried out in duplicate and assessed using the key data variables. Selection of data will be carried out by two independent researchers, in order to extract the most specific literature for the review following the phases on the PRISMA statement.[14]

During the keyword search, keywords will be combined into a phrase including Boolean (AND, OR) terms, and including MeSH (Medical Subject Headings) terms, as in the sample demonstrated below (as this will be an iterative process and will be documented in the analysis and write up):

("(hiv infected women) OR hiv positive women) AND point of care diagnostics) OR point of care testing) OR rapid testing) OR laboratory testing) OR laboratory diagnostics) AND reduced maternal mortality) OR (prevention of maternal to child transmission)) OR successful linkage to continuity of hiv care) OR initiation of

Table 1 A PICOS framework for determination of the eligibility of the studies for the primary research question

Criteria	Determinants
P—Population	HIV-infected women
I—Intervention	Diagnostic algorithm using POC testing to detect HIV and HIV-related infections for maternal patients, which will include the following: ▶ HIV screening ▶ CD4 tests ▶ Viral load tests ▶ TB tests ▶ Syphilis screening test
C—Control	Diagnostic algorithms based on conventional laboratory tests to detect and manage HIV and HIV-related infections in maternal patients
O—Outcome	*Primary outcome*: Reduction of maternal mortality *Intermediate outcome*: Timely receipt of test results or diagnosis *Secondary outcomes*: Prevention of maternal and child transmission; successful linkage to HIV care and ART initiation; maternal and child morbidity and partner testing
S—Study design	Individual or cluster randomised controlled trials, non-randomised clinical trials, observational studies

ART, antiretroviral therapy; POC, point of care; TB, tuberculosis.

antiretroviral treatment") OR maternal morbidity") OR infant morbidity") OR partner testing") OR timely receipt of test results") OR timely receipt of test")

All researchers will keep an updated record of the number of publications identified and date of each session of literature search (table 2).

Stage 2: Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed to ensure a sufficient level of comparability across HIV-related POC diagnostic interventions and laboratory-based HIV-related diagnostics.

Inclusion criteria

- Evidence published in the English language
- Evidence from published global randomised controlled trials (RCTs), non-randomised clinical trials, observational studies of HIV-related diagnostic interventions
- All of the criteria defining the POC diagnostic intervention had to be met for an empirical study
- Empirical evidence examining the impact of POC diagnostics and laboratory-based intervention or non-POC diagnostic independent from any broader intervention impact
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on maternal mortality on HIV-positive women will be included
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on reduction of maternal mortality
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on prevention of maternal and child transmission
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on successful linkage to continuity of HIV care
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on start of ART treatment
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on prevention of HIV vertical transmission
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on reduction of maternal and child morbidity
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' impact on partner testing
- Evidence about POC diagnostics and laboratory-based or non-POC diagnostic interventions' allowing timely receipt of test results or diagnosis

Exclusion criteria

- Study which does not have the outcomes of interest as objectives
- Case reports, expert opinions and review/meta-analysis
- Evidence published before the year 2000
- Evidence from the HIV-negative patients will be excluded because the impact of HIV-related diagnostic intervention is expected to be substantially different from that in our target group
- Evidence where the impact of HIV-related diagnostic intervention could not be differentiated from the impact of a broader intervention
- Evidence aimed at assessment on HIV-related diagnostic knowledge, skill and attitude level
- Evidence on cost-effectiveness of POC diagnostics
- Evidence on POC diagnostics user and patient's perceptions.

Table 2 Electronic search record

Date	Keyword searched	Search engine used	Number of publications retrieved

DATA COLLECTION AND ANALYSIS

Selection of studies

The studies will be selected by evaluation of the inclusion and exclusion criteria. This will be carried out in duplicate and independently by two authors with agreement assessed using κ statistics.

Assessment of risk of bias in included studies

The authors will assess and judge the quality of the selected papers using the Cochrane risk of bias tool.[16] Bias will be assessed against the following items:

- How the allocation sequence was generalised;
- How allocation was concealed from participants, investigators and outcomes;
- Blinding of participants and investigators;
- Blinding of outcome assessors;
- Completeness of outcomes data (number analysed relative to number randomised);
- Selective reporting: whether all prespecified outcomes are reported.

Measure of diagnostic effect

For all included outcomes, we will calculate a risk ratio and present the results alongside the 95% CI.

Unit of analysis issues

We will perform analysis of all outcomes at individual-study level, using a generic inverse variance method. Meta-analysis and subgroup analysis will be conducted using Review Manager (*RevMan*)[16] with Stata 13 being used for any meta-regression. To address the unit of analysis issues in cluster randomised trials, intracluster correlation coefficient (ICC) or ρ will be determined.[17] The outcome ICC and adjustment for cluster correlation can be assessed using a clustered analysis of variance

(ANOVA) method with bootstrapped 95% CIs. This can be implemented in Stata.[18] Furthermore, a random-effects meta-regression will also be employed to account for the clustering effect. Again, this can be implemented in Stata. Restricted maximum likelihood estimation will be used ('metareg').[19]

Dealing with missing data

The missing data in this review will be dealt with in the following manner:

- Whenever possible, the original investigators will be contacted to request missing data.
- The assumptions of any methods used to cope with missing data will be made explicit: for example, that the data are assumed missing at random or that missing values were assumed to have a particular value such as a poor outcome.
- Sensitivity analyses will be performed to assess how sensitive results are to reasonable changes in the assumptions that are made.
- The potential impact of missing data will be addressed on the findings of the review in the discussion section.

Assessment of heterogeneity

We will assess heterogeneity among trials by inspecting the forest plots for overlapping CIs. We will also apply the χ^2 test for the heterogeneity of a 10% level of statistical significance and an I^2 statistic value >40% to denote moderate levels of heterogeneity.[16]

Data synthesis

The data will be analysed using Review Manager (*RevMan*) 5.3 software. The generic inverse variance method will be used for meta-analysis of both, individually and cluster randomised trials. In a case where we do not find at least two studies to produce a single estimate of the effect of HIV-related POC diagnostics on the desired outcomes for this study, and it is deemed impossible to perform meta-analysis, subgroup analysis and sensitivity analysis will be implemented.

Quality and strength of evidence

The quality of the evidence will be assessed across each outcome measure, using the GRADE approach.[20] The quality rating across trials will be for levels: high; moderate; low or very low. RCTs are categorised as high quality but can be downgraded after assessment of the following five criteria: risk of bias; consistency; directness; imprecision and publication bias.[20]

Subgroup analysis and investigation of heterogeneity

Where heterogeneity is detected, researchers will perform subgroup analyses by stratifying the results according to the target group. Variables such as: type of study design (individual vs cluster randomisation RCTs) will be used to explain heterogeneity a priori. In a case where we do not find at least two studies to produce a single estimate of the effect of point-of-care testing of the desired outcomes for this study, and it is deemed impossible to perform meta-analysis, subgroup analysis and sensitivity analysis will be implemented. In addition, a statistical heterogeneity test with χ^2 will be carried out. Subgroup analysis will be used to investigate the level of heterogeneity in the included studies. In heterogeneity analysis, a low r value will provide evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance).

Sensitivity analysis

A repeat of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear, will be carried out by all researchers to ensure that findings of the systematic review are robust to the decisions made in the process of obtaining them.

Detailed evidence tables will be prepared to describe the methodological quality of each study, details of the intervention or aspect of community health worker intervention examined, study site/population and findings. Reviewers will read and re-read data contained within the evidence tables, apply codes and memos to capture the content of the data, and then group and organise codes into higher-order themes. These themes will be used to generate an explanatory framework to address research aims. In all cases, where there is a danger of missing data affecting our analysis, we will contact the authors of papers, wherever possible, to request additional information.

Finally, we will draw on our individual syntheses to produce a draft report. We will then organise stakeholder meetings to review our key findings and conclusions. Taking on board the views expressed by stakeholders, we will then finalise our technical report and executive summary, and begin disseminating the research via other means.

Ethics and dissemination

Ethical approval will not be needed because the data used in this systematic review will not be individual patient data, and there will be no concerns about privacy. The results will be disseminated by publication of the manuscript in a peer-reviewed journal and presented at a relevant conference.

DISCUSSION

The extent of the contribution of HIV/AIDS to maternal mortality is difficult to quantify, as the HIV status of pregnant women is not always known.[21] Recent studies have demonstrated that the mortality rate of HIV-infected women is nearly 10 times the rate of their HIV-uninfected counterparts.[5 22 23] Many of these deaths are believed to be preventable with the implementation of high-quality obstetric care, prevention and treatment of common co-infections, and appropriate

ART regimens.[24] Diagnostics are a fundamental component of medical practice. Early disease diagnosis is key to the improvement of disease prognosis, particularly in the current era of drug resistance.[25 26]

Several new POC diagnostic platforms have been specifically designed to assist clinical staff, replacing the equivalent laboratory tests and allowing diagnoses to be performed immediately at the POC.[27–29] Many existing systematic reviews[30–33] focus on the effect of HIV-related POC diagnostics for HIV-infected and HIV-uninfected men and women. Although the use of POC diagnostic interventions has been shown to improve linkage to care,[32] improve uptake of perinatal HIV care[31] and reduce the time to eligibility assessment for ART; and though it is highly accurate compared with conventional tests,[33] increases pre-ART retention in care[30] and improves maternal, infant morbidity and partner testing,[8] it is currently not known whether it provides impact to overall maternal health outcomes (reduction of maternal mortality, prevention of maternal and child transmission, successful linkage to HIV care and ART initiation, improvement of maternal and child morbidity, and partner testing) for HIV-infected women.

This is the first systematic review that attempts to investigate the impact of POC diagnostics on maternal outcomes for HIV-infected women. In light of the current upsurge of research and publications on the topic, the contribution of a systematic review gains importance and relevance by attending to this knowledge gap. The aim of this study is to carry out a systematic review of previous and current POC testing RCTs, non-RCTs and observational studies to determine whether HIV-related POC diagnostics, compared with conventional laboratory testing, improves maternal health outcomes for HIV-positive women.

As evident in previous studies, maternal outcomes of HIV-negative women are substantially different from those in our target group; therefore, evidence on POC diagnostics maternal outcomes of HIV-negative women will be excluded from this study.[5 22 23] To ensure reliability of our study findings, evidence where the impact of HIV-related diagnostic intervention could not be differentiated from the impact of a broader intervention will also be excluded. User and patients' level of cost, knowledge, skill and attitude towards POC diagnostics has been reported to have an impact on the acceptability and utility as well as accuracy of POC diagnostics.[34–36] However, in order to gain a more quantitative view of the impact of POC diagnostics on the target group, evidence from qualitative studies and cost-effectiveness studies of POC diagnostics will be excluded.

We anticipate finding a large number of studies missed by previous reviews; and that HIV-related diagnostic intervention studies examine a greater breadth of determinants that addresses HIV-related POC diagnostic impacts on maternal outcomes in HIV-positive women. Evidence will be limited to the English language published literature due to lack of capacity and funding for language translation. This may have an impact on the number of studies (particularly RCTs) as it excludes eligible studies that are published in languages other than English. Therefore, our study is not limited to RCT studies—it has included non-RCTs and observational studies in the study design eligibility criteria. This systematic review will provide a general overview and evidence of the impact of POC diagnostics on maternal health for HIV-infected women. The results of this review will provide useful information to guide health policy—and to influence decision-makers, developers of POC diagnostics and maternal health healthcare workers—on improved implementation of future POC diagnostics so as to improve maternal health outcomes for HIV-infected women.

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Contributors TPM-T conceptualised and designed the study, and prepared the draft of the research proposal under the supervision of BS and PKD. TPM-T and LT contributed to developing the background and planned output of the review, designing of the study—particularly the methods relating to review and synthesis of data—as well as design of the sifting and data extraction processes. LT, PKD and CXS assisted with the manuscript preparation. All the authors reviewed draft versions of the manuscript and approved the final version of the manuscript.

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