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Interventions for preventing mother-to-child HIV transmission: protocol of an overview of systematic reviews

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ABSTRACT

Introduction Various interventions to prevent mother-to-child-transmission (MTCT) of HIV have been investigated and implemented. A number of systematic reviews assessing the efficacy of interventions for the prevention of MTCT of HIV reported antiretroviral prophylaxis, caesarean section before labour and before ruptured membranes, and complete avoidance of breastfeeding were efficacious for preventing MTCT of HIV. Recent WHO guidelines recommend lifelong antiretroviral therapy for all pregnant women for treatment of the woman's own HIV infection and for prevention of MTCT of HIV. Therefore, the objective of this overview is to evaluate the currently available systematic reviews of interventions for preventing MTCT of HIV, and to identify the current best evidence-based interventions for reducing the risk of MTCT of HIV.

Methods and analysis We will include only peer-reviewed systematic reviews of randomised or quasi-randomised controlled trials assessing the effects of interventions for preventing MTCT of HIV that target both HIV-infected women and children aged 2 years and younger born to HIV-infected women. We will search the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, Ovid MEDLINE and EMBASE. We will assess review eligibility, the methodological quality of included systematic reviews using A Measurement Tool to Assess The Systematic Reviews and will extract data, comparing our results and resolving discrepancies by consensus. Finally, we will independently assess the certainty of the evidence using Grades of Recommendation, Assessment, Development and Evaluation.

Ethics and dissemination Ethics approval is not required. We will publish the results in a peer-reviewed journal and present at conferences, which will inform future research and will be useful for healthcare managers, administrators and policymakers to guide resource allocation decisions and optimisation of interventions to prevent the MTCT of HIV.

Strengths and limitations of this study

- This overview will provide the current best systematic reviews of interventions to prevent mother-to-child-transmission (MTCT) of HIV, after a decade has passed since the publication of the first overview.
- We will use validated protocols and assessment tools for search methods, data extraction, methodological quality assessment, grading of certainty of evidence and reporting.
- We will include all systematic reviews of randomised or quasi-randomised controlled trials of interventions aimed at reducing the MTCT of HIV from various databases.
- A limitation of this overview is that it will include only published systematic reviews. Therefore, it is possible that more recent randomised controlled trial evidence would not be incorporated in this overview, if it is not included in published systematic reviews.

INTRODUCTION

An estimated 1.8 million (range 1.5–2.0 million) children under the age of 15 years were living with HIV infection or AIDS worldwide at the end of 2015.[1] Most HIV-infected children acquire their infection through mother-to-child transmission (MTCT). MTCT of HIV occurs during three time periods: in utero (during pregnancy), intrapartum (around the time of labour and delivery) or postnatally through breast milk.[2 3] Pregnancy and the postpartum period account for the largest potential for persistent HIV transmission risk.[4] Over 40% of MTCT occurs through breast milk transmission.[5]

Various interventions to prevent MTCT of HIV have been investigated and implemented, particularly in low-income and middle-income countries. A 2007 'umbrella review' of five separate Cochrane reviews assessed the efficacy of several interventions for the prevention of MTCT of HIV.[6] Of these interventions, antiretroviral (ARV) prophylaxis and caesarean section before labour and before ruptured membranes were efficacious for preventing MTCT of HIV.[7 8] A systematic review included in this overview found complete avoidance of breastfeeding to be efficacious.[9] Several interventions, such as maternal or infant cleansing with

chlorhexidine, vitamin A supplementation and hyperimmune HIV immunoglobulin were not found to be efficacious in preventing MTCT of HIV.[10–12]

Observational studies have suggested a lower risk of MTCT of HIV among exclusively breastfed infants compared with infants with mixed breastfeeding (eg, formula and breast milk).[13 14] An intervention cohort study provided evidence for the association of exclusive breastfeeding with a lower risk of MTCT of HIV compared with mixed feeding.[15] Exclusive breastfeeding is associated with fewer breast health problems such as mastitis and breast abscesses, which might increase the viral load of the HIV-infected mother's breast milk.[16] Particularly in resource-limited settings, exclusive breastfeeding provides safer feeding for infants.[17 18] In general, breastfeeding protects against many infectious diseases, primarily respiratory infections and diarrhoea, and reduces infant and child mortality.[19]

In 2013, WHO announced guidelines for using antiretroviral therapy (ART) in all HIV-infected pregnant and breastfeeding women regardless of CD4 or clinical stage.[20] The WHO guidelines recommend that ART should be maintained at least for the duration of MTCT risk, with the option of continuing lifelong ART for all pregnant and breastfeeding women (option B+).[20]

Why it is important to do this overview?

Our goal is to collate all evidence-based interventions for reducing the risk of MTCT of HIV from various databases, and to provide accurate evidence and recommendations for healthcare policymakers and researches. Various interventions and strategies have been developed and implemented to reduce MTCT of HIV. In high-income countries, use of ARVs by HIV-infected women, caesarean section before labour and before ruptured membranes, and complete avoidance of breastfeeding are used for prevention of MTCT of HIV. However, in low-income countries, where caesarean section before labour and before ruptured membranes and complete avoidance of breastfeeding are not generally feasible, interventions for prevention of MTCT of HIV are more limited. In such settings, ARVs for HIV-infected women and/or their infants while breastfeeding and exclusive breastfeeding are strongly recommended.[21] Several systematic reviews have assessed a number of interventions aimed at reducing MTCT of HIV and have shown the evidence for what works, what does not work, what could be harmful and where more research is crucially needed. Previously, a 2007 'umbrella' overview review, a systematic review of all Cochrane reviews of PMTCT interventions, examined interventions for preventing MTCT of HIV and summarised the evidence for the efficacy of ARV prophylaxis and for caesarean section before labour and ruptured membranes in reducing the risk of MTCT of HIV.[6] This umbrella overview had the limitation that it only included Cochrane systematic reviews. In addition, a decade has passed since the publication of the previous overview, and new systematic reviews of various interventions to prevent MTCT have been published. Moreover, WHO recently recommended ART for pregnant and breastfeeding women for treatment of women's HIV infection and for prevention of MTCT of HIV. This overview, therefore, will inform judgements, optimisation and future research about the available evidence-based interventions to prevent MTCT of HIV.

OBJECTIVES

The objective of this overview is to evaluate and summarise the evidence from systematic reviews of interventions for preventing MTCT of HIV, to identify the current best evidence-based interventions for reducing the risk of MTCT of HIV, and to help inform judgements, optimisation and future research about the available evidence-based interventions to prevent MTCT of HIV.

METHODS AND ANALYSIS

Protocol and registration

This protocol was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist (see online Supplementary material).[22] This protocol is registered on the International prospective register of systematic reviews (PROSPERO), registration number: CRD42017042367.

Criteria for considering reviews for inclusion

Type of reviews

We will include only published peer-reviewed systematic reviews of randomised or quasi-randomised controlled trials.

Type of participants

We will include systematic reviews that target HIV-infected pregnant or breastfeeding women (as diagnosed by biological testing) at any age, any clinical stage of HIV disease and any setting, and children aged 2 years and younger born to HIV-infected women.

Type of interventions

We will consider all types of interventions that may prevent MTCT of HIV, including (but not limited to) ARVs for the mother and/or for the infant, ART for pregnant and breastfeeding women, and infant feeding modality interventions.

Type of outcome measures

We will consider the systematic reviews with the following outcomes:

1. Primary outcomes:
   - Efficacy of the intervention;
   - Acceptability of the intervention;
   - Overall survival of the child;
   - HIV-free survival (as defined by trials); including:
     - HIV infection status of the child at birth, at 2 weeks, 4–8 weeks, 3–4 months, and at 6, 12 and 18 months;

- Child death at 2 weeks, 4–8 weeks, 3–4 months and at 6, 12 and 18 months of age.

2. Secondary outcomes:

i. Maternal outcomes:
- Maternal mortality at 1 and 2 years, and later time points when available;
- Severe adverse events (except death) including: hepatotoxicity in women given nevirapine (NVP) (CD4 250–350 cells/mm^3 and >350 cells/mm^3), renal toxicity with tenofovir, all other grade 3 or 4 severe adverse events;
- Development of maternal resistance resulting in ARV discontinuation or virological failure (as defined by the authors);
- Adherence to and tolerability of ARV regimens, and retention in care; cost of the intervention, if required.

ii. Infant outcomes:
- Stillbirth rates;
- Severe adverse events, including: low birth weight (<2500 g), very low birth weight (<1500 g); preterm birth (<37 completed weeks of gestation), very preterm birth (<34 completed weeks of gestation);
- Congenital anomalies; neonatal sepsis (as defined by the authors);
- Admission to intensive care unit;
- Long-term adverse events and other adverse events in the child (as defined by the authors).

Search methods for identification of reviews

We will conduct searches in electronic databases using a combination of keywords and Medical Subject Heading (MeSH) terms, which are '('HIV Infections' OR HIV OR hiv OR 'human immunodeficiency virus') AND ('Infectious Disease Transmission' OR 'mother-to-child transmission' OR MTCT OR 'maternal and transmission' OR 'fetomaternal transmission') AND (prevention OR prevent OR 'Prevention and control' OR PMTCT OR PMCT') AND ('systematic review' OR review OR 'review of reviews') AND ('meta-analysis' OR 'meta-review')' in title, abstract or keyword. We will search the following electronic databases, adapting the search strategies as appropriate for each database: Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, Ovid MEDLINE and EMBASE (detailed search strategy is reported in the online Supplementary appendix 1). We will not apply any language restrictions. The date range of search will start from inception to the search date.

Data collection and analysis

The methodology for data collection and synthesis for this overview will be based on and guided by Chapter 22 of the Cochrane Handbook of Systematic Reviews of Interventions.[23] This chapter gives criteria for conducting overviews of systematic reviews.

Selection of reviews

Two authors (WMVW and EO) will independently screen the search output for potentially eligible systematic reviews, followed by independent duplicate assessment of the full text of potentially eligible reviews for inclusion in the overview. Criteria for inclusion will be based on the type of studies, type of participants, type of interventions and type of outcome measures. The two authors will resolve any disagreement through discussion to arrive at the consensus and, if needed, they will consult a third author.

Data extraction and management

We will summarise each included systematic review using an approach developed by the Supporting Policy-relevant Reviews and Trials (SUPPORT) Collaboration.[24] Two authors will independently perform data extraction from the included systematic reviews using an electronic standardised spreadsheet data extraction form to record descriptive characteristics of included reviews. We will resolve all discrepancies through discussion between the two authors, and consensus, failing which a third author will arbitrate. We will extract and tabulate bibliographic and administrative information for each systematic review. We will extract the following: characteristics of the review including first author name, year of publication, review title, search date, the number of included studies; characteristic of the population demographics, settings; type of the interventions and their comparison; type of outcomes; the key findings; quality of included; considerations for applicability in both high-income, and middle-income and low-income country settings and other important information of what the authors found.

We will also perform full data extraction from systematic reviews reporting a pooled effect estimate resulting from meta-analysis including risk ratios, ORs, mean differences, standardised mean differences or number needed to treat. We will rank the effectiveness of intervention effect size against other interventions or no intervention.

Certainty of evidence in included reviews

We will assess the certainty of evidence for primary and secondary review outcomes using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach as outlined in the GRADE handbook.[25] We will report the certainty of evidence as assessed by the systematic review authors. If the systematic review authors did not assess the certainty of the evidence, we will use GRADEPro Guideline Development Tool[26] to assess the certainty of the evidence reported by the review authors.

Methodological quality of included reviews

Two authors will independently assess the methodological quality of the included systematic reviews

using the A Measurement Tool to Assess the systematic Reviews (AMSTAR) instrument, a tool with good construct validity and reliability.[27] AMSTAR evaluates the methods used in a review against 11 distinct criteria relating to the assessment of methodological rigour, and also assesses the degree to which methods are unbiased. Each item on AMSTAR is scored as 'yes', 'no', 'cannot answer' or 'not applicable'.

We will then categorise each included systematic review, using criteria developed by the SUPPORT Collaborations[28] as having: only minor limitations; limitations that are important enough that it would be worthwhile to search for another systematic review and to interpret the result of this review cautiously, if we cannot find a better systematic review; limitations that are important enough to make the finding of the systematic review unreliable and the review should not be included in the overview.

Data synthesis and presentation

We will provide narrative summaries of the relevant results for the individual systematic reviews for each of the primary and secondary outcome measures by intervention. We will present the summary using tables and figures as 'Overview of reviews table', including the characteristics of included systematic reviews, the certainty of evidence within individual systematic reviews and results by individual systematic reviews using AMSTAR rating. We will also prepare a table of excluded systematic reviews that will describe the characteristics of excluded reviews and their reasons for exclusion.

Summary of findings

We will create 'Summary of finding' for the main comparison tables using the GRADE profiler Guideline Development Tool. We will use the GRADE approach[26] to assess the overall certainty of the body of the evidence relating to primary and secondary outcomes for the main comparison.

DISCUSSION

This overview will be the first summary of existing systematic reviews and other databases of interventions from randomised or quasi-randomised controlled trials of interventions aimed at reducing MTCT of HIV. We will incorporate all other potential relevant considerations besides the findings of the included systematic reviews when drawing conclusions about implications for practice and research. The conclusions will be based on types of interventions and finding of the included reviews. This overview, therefore, will help healthcare policymakers to implement the most effective interventions to prevent MTCT of HIV, and for researchers to design high-quality studies of the available evidence-based interventions.

Contributors WMVW, EO and RM designed, set up and drafted the protocol. JSR, CSW and HH revised and supervised development of the protocol and made several substantive edits and suggestions. All authors read and approved the final protocol.

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