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Risk of transmission of HIV to infants during breast/chest feeding when mothers/birthing parents living with HIV are on antiretroviral therapy: a protocol for a rapid review

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ABSTRACT

Introduction HIV is a major public health issue affecting millions globally. Women and girls account for 46% of new HIV infections in 2022 and approximately 1.3 million females become pregnant every year. Vertical transmission of HIV from persons living with HIV (PLHIV) to infants may occur through different modalities, such as through breast/chest feeding. Notably, 82% of PLHIV who chose to breast/chest feed are on antiretroviral therapy (ART) when feeding their infants. Precise estimates of the risk of postpartum transmission to infants during breast/chest feeding at varying viral load levels remain a significant gap in the literature.

Methods and analysis A rapid systematic search of electronic databases will be conducted from January 2005 to the present, including Medline, Embase and Global Health. The objective of this rapid review is to explore and assess the available evidence on the effect of varying viral load levels on the risk of HIV transmission to infants during breast/chest feeding when the birthing or gestational parent living with HIV is on ART. Study characteristics will be summarised and reported to support the narrative summary of the findings. The focus will be on the absolute risk of HIV transmission from birthing parent to infant during chest/breast feeding. The findings will also be stratified by month, including the risk of HIV transmission for 6 months and greater than 6 months postpartum. We will ascertain the risk of bias using A Measurement Tool to Assess Systematic Reviews 2, Quality of Prognosis Studies and Downs and Black checklist for the appropriate study type. A summary score will not be calculated, rather the strengths and limitations of the studies will be narratively described.

Ethics and dissemination No human subjects will be involved in the research. The findings of this rapid review will inform a future systematic review and will be disseminated through peer-reviewed publications, presentations and conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This rapid review will collect evidence in a shorter amount of time which could inform policy and health decision-making.
⇒ This review will provide evidence to strengthen the undetectable equals untransmittable (U=U) and treatment as prevention messaging and prevention campaigns around HIV stigma.
⇒ Relevant information could be missed due to the streamlined processes of a rapid review.
⇒ The lack of a rigorous and quality appraisal of studies could cause incomplete reporting of available evidence.
⇒ The study will not address infants maintained on antiretroviral prophylaxis while breast/chest feeding.

INTRODUCTION

In 2022, the global estimate of the number of children under the age of 15 living with HIV was 1.5 million. Furthermore, 53% of all persons living with HIV were women and girls which accounted for 46% of new infections in 2022. An estimated 1.3 million women and girls living with HIV become pregnant every year. Also, globally the proportion of those who are pregnant or breast feeding living with HIV who have access to antiretroviral therapy (ART) has increased from 48% in 2010 to 82% (64%–98%) in 2022.[1 2] This has translated to a 58% decline in new HIV infections among children during the same period.[2] The Global AIDS Monitoring framework 2022–2026 aims to eliminate the risk of a person living with HIV (PLHIV) transmitting HIV to their child (vertical transmission) and ensure that 86% of all children living with HIV have suppressed viral load by 2025, and that all pregnant and breastfeeding women living with HIV are receiving lifelong ART, with 95% achieving and sustaining viral suppression before delivery and during breast feeding by 2025.[3]

Mother to child transmission of HIV can occur in utero, intrapartum and during breast/chest feeding. In utero, HIV crosses the placenta resulting in a newborn infected with HIV, which can be confirmed by an HIV nucleic acid amplification test (NAAT) or PCR of the newborn's blood within 48 hours of delivery.[4] Infants may be infected intrapartum through skin or mucosal membrane contact with cervical secretions and blood of the birthing parent during delivery and can be diagnosed with NAAT at approximately 4–6 weeks after birth.[5 6] Lastly, HIV can be transmitted postpartum through breast/chest feeding which is the area of interest of this study.[4] Infants are considered to be infected during the postpartum period (due to breast/chest feeding) if the HIV NAAT or PCR is negative at birth and at approximately 4–6 weeks after birth, but is positive at 6, 9 or 12 months.[6 7]

Breast feeding offers infants a multitude of benefits that improve overall health including the decrease in the risk of childhood cancer, fewer gastrointestinal infection and less respiratory infections.[8] Furthermore, among other benefits, breast feeding is associated with improved neonatal immune status and a lower risk of infants developing asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome and necrotising enterocolitis. Breast feeding also provides parental benefits and facilitates bonding with the infant which could lower the incidence of parental depression and anxiety.[8–10] In recognition of these benefits, WHO promotes that mothers living with HIV on ART should exclusively breast/chest feed for at least 6 months.[11] The US dietary guidelines also recommend that infants be exclusively breastfed for about 6 months. Breast feeding could then continue while introducing appropriate complementary foods until the infant is 12 months or older.[9]

ART lowers the HIV viral load of the gestational parent, thus reducing their risk of transmission of HIV to their infants.[7] Following 2 years of breast feeding, the risk of HIV transmission from the birthing parent to the infant is approximately 15%–20% without the use of ART.[12 13] In a 2017 systematic review, Bispo *et al* conducted a meta-analysis of 11 studies published between 2005 and 2015 and reported an infant postnatal HIV infection risk of 1.08% (95% CI 0.32% to 1.82%) up to 6 months of age when the birthing parent was living with HIV and had been on prolonged ART. A higher risk was reported when the birthing parent started ART in the late stage of pregnancy.[7] Furthermore, maternal HIV viral load and drug resistance have been associated with breast/chest feeding infant HIV transmission.[14] A systematic review performed by PHAC in 2018 and updated in 2023 examined the risk of sexual transmission of HIV when the PLHIV was on ART with varying viral load levels, including levels <200 copies/mL.[15 16] PHAC concluded with high certainty of evidence that the risk of sexual transmission of HIV is low when the PLHIV is on ART with varying levels of viral load and negligible if the PLHIV is taking ART with a viral load of less than 200 copies/mL with consecutive measurements every 4–6 months.[16] These findings raised the question of generalisability towards postpartum vertical transmission risks conditional on VL levels.[17] New evidence on the estimated risk of post partum, breast/chest feeding-related HIV transmission to an infant from a birthing parent on documented ART and followed with viral load measurements is important and currently lacking.

Previously published reviews have highlighted the considerable methodological heterogeneity in studies characterised by differences in the time of ART initiation during pregnancy, the recommended duration of breast feeding, the age at which infection in the infant was assessed, the details on infant feeding modality and the definition of postnatal transmission.[18 19]

We hypothesise that the risk of vertical transmission of HIV to infants during breast/chest feeding will be very low or negligible when the birthing or lactating parent living with HIV is on ART. Most of the global literature suggests that viral suppression during pregnancy decreases the risk of HIV transmission to breastfeeding infants to less than 1%, but not zero,[6 20–23] while some recent studies conducted in high-income countries reported zero transmissions.[24 25] The 2023 US guidelines recommend that people living with HIV on ART with consistent viral load suppression during pregnancy should be counselled on the various options of breast feeding, formula feeding, mixed feeding or banked donor milk.[6]

The objective of this rapid review is to explore and assess the new available evidence on the estimated effect of varying viral load levels on the risk of HIV transmission to infants during breast/chest feeding when the birthing or lactating parent living with HIV is on ART.

Terminology and definitions

In this article, breast/chest feeding refers to the gestational, birthing or lactating parent providing milk from their own body to the infant from the breast or chest. Furthermore, breast/chest feeding will be defined in this study as exclusive breast/chest feeding or mixed feeding. To adhere to previous literature and Joint United Nations Programme on HIV/AIDS (UNAIDS) terminologies and depending on the context, we will alternatively use women, mother and girls throughout the manuscript.[2 3]

Research questions

The following questions will be addressed:

Question 1: What is the risk of HIV transmission to infants from breast/chest feeding when the lactating parent is living with HIV and is on ART and maintains a viral load <200 copies/mL?

Question 2: What is the risk of transmission of HIV to infants from breast/chest feeding when the mother is living with HIV and is on ART with varying viral load levels >200 copies/mL?

Table 1 List of inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
A. Population	▶ Infant not infected with HIV at birth and at 4–6 weeks after birth.	▶ PLHIV not on ART ▶ HIV status of infant infected or not assessed at birth or at 4–6 weeks after birth
B. Intervention	▶ Mother living with HIV on ART ▶ Exclusive breast/chest feeding ▶ Mixed feeding	▶ Birthing/lactating parent exclusive formula feeding. ▶ Pasteurised donor human milk ▶ Mother LHIV not on ART ▶ Mother developing mastitis or bleeding nipples
C. Comparator	Any; including infants taking HIV medication at birth.	None
D. Outcomes	Report one or more of the following outcomes: ▶ Assessment of infant HIV infection post partum (after 4–6 weeks postdelivery) ▶ Mother HIV viral load measurement using plasma sample.	▶ HIV outcome not assessed in infant after 4–6 weeks post partum. ▶ Infant HIV infection at birth or during peripartum period ▶ No maternal HIV viral load measurements
E. Timing	▶ Timing of ART initiation by mother/birthing parent: before pregnancy, antepartum, peri partum, post partum ▶ Timing of viral load measurement in mother/birthing parent	
F. Study design	▶ Experimental studies (randomised and non-randomised controlled trials) ▶ Observational studies ▶ Retrospective and prospective cohort studies ▶ Studies with or without a comparison group ▶ Studies published in English and French	▶ Articles that are unrelated to the research question ▶ Narrative reviews ▶ Scoping reviews ▶ Commentaries ▶ Conference abstracts ▶ Editorials

ART, antiretroviral therapy; PLHIV, persons living with HIV.

METHODS

Patient and public involvement

In designing this rapid review, neither patients nor the public were involved.

Data sources and searches

This study will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards whenever possible. An extension to PRISMA for Rapid Reviews is underway,[26] so the general PRISMA statement will be used.[27 28] Therefore, to report this protocol, we will use an adapted version of the PRISMA protocols (online supplemental appendix 1).[29]

We will systematically search Medline (via Ovid), Embase (via Ovid) and Global Health (via Ovid) for systematic reviews and peer-reviewed articles from 1 January 2005 to 1 November 2023. This is consistent with the work of previous systematic reviews who restricted the selection of studies from 2005 or later because triple combination ART regimens were introduced in public health programmes in 2004.[30 31] Search types and patterns are featured in online supplemental appendix 2.

Study selection

Studies will be eligible for inclusion (table 1) if the PLHIV was on ART and breast/chest feeding. Studies also need to be published in English or French and assess the HIV status of infants. The time (antepartum, peripartum or post partum) that the PLHIV began ART, and frequency or intervals of viral load measurements and levels must be reported. Our outcome of interest is infant HIV diagnosis post partum due to breast feeding, and therefore, studies need to report that infants were not diagnosed with HIV acquired in utero or peripartum (confirmed by a negative HIV NAAT post partum, at approximately 4–6 weeks of age).

Viral load needs to be measured through plasma testing since that is the clinical standard of care.[32] We will exclude articles that are unrelated to the research questions, narrative reviews, scoping reviews, commentaries, conference abstracts and editorials. Table 2 shows the population, intervention, comparator, outcomes, setting and time or this rapid review.

Screening and study selection

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) will be used for the removal of duplicates and screening of articles. Reviewers (GB, JD and PVN) will perform a pilot screening with a sample of 100 and abstracts to ensure consistency of use and clarity of the inclusion and exclusion criteria.[28] To measure inter-rater reliability, a Cohen's kappa statistic will be calculated.[33] The screening will begin when more than 70% agreement will be achieved. In duplicate, the authors (GB, JD and PVN) will conduct all screening, data extraction and quality assessment procedures. Disagreements will be resolved by consensus. Situations where consensus cannot be reached will be resolved by a third author who will arbitrate (PD and HB). Eligible articles identified by title and abstract screening based on inclusion criteria will be selected for full-text screening. Two independent reviewers will review the full texts. References of the included studies will be handsearched to

Table 2 Population, intervention, comparator, outcomes, setting and time (PICOST)

PICOST	Description
Population	Birthing or lactating parent living with HIV, on ART and their infant is breast fed with no HIV infection in the antepartum or peripartum period.
Intervention/exposure	Mother or lactating parent living with HIV on ART with measurement of viral load levels and, if possible, timing and duration at different viral load levels. Exclusive or mixed breast/chest feeding of infant at birth.
Comparator	Any or none (including infant taking HIV medication at birth)
Outcomes	Incidence of infant HIV infection post partum due to breast or chest feeding and, if possible, timing of infection since birth and duration of exposure at transmission.
Setting	Any settings.
Time	Studies since 2005

ART, antiretroviral therapy.

identify additional relevant studies for inclusion. Conflicts between reviewers will be resolved through consensus, and if no resolution can be achieved, a third reviewer (PD and HB) will be consulted. In case of missing data or information, authors will be contacted.

A third reviewer (PD and HB) will confirm the excluded publications and their respective reasons for elimination.[27] The PRISMA 2020 flow diagram (figure 1) will be used to show the process of study selection.[27]

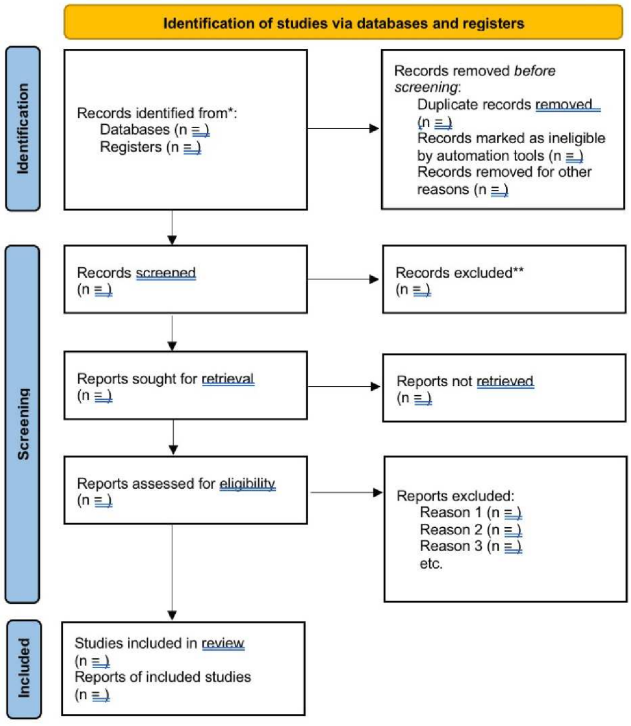

Figure 1 PRISMA flow diagram example. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data extraction and quality assessment

After the full-text screening and study selection process, the selected studies will undergo data extraction, wherein information from the studies will be extracted after a thorough reading of the full text. The list of variables to be extracted is presented in table 3. The data extraction form will be created using Microsoft Excel 2016. Data extraction will be conducted by two independent reviewers using the designed data extraction form. Following this process, the records extracted by the reviewers will be cross-checked, and any disputed points will be resolved through a third reviewer (PD and HB).

Summarising and reporting

Eligible studies will be identified and included based on the inclusion and exclusion criteria (table 1). Reviewers will abstract relevant data from included studies into tables. Study characteristics will be summarised and reported to support the narrative summary of the findings, focusing on the absolute risk of HIV transmission from mother to child during breast/chest feeding. Findings of studies will be also stratified by month, including risk of HIV transmission for 6 months and for more than 6 months post partum. The limitations of the included studies reported by study authors will be summarised and reported.

Risk of bias of individual studies

Each included systematic review will be evaluated for quality or risk of bias using A Measurement Tool to Assess Systematic Reviews 2 tools.[34] Quality of Prognosis Studies instrument and Downs and Black Checklist will be used to evaluate risk of bias on prognosis and randomised controlled trial (RCT)/non-RCT studies, respectively.[35 36] Summary score will not be calculated, rather the strength and limitation of the studies will be narratively described.

Ethics and dissemination

Ethics approval will not be required for this rapid review's protocol. The findings of the review will be disseminated through peer-reviewed publications, presentations and

Table 3 List of variables for data extraction

PICO components	List of variables
Basic study characteristics	▶ Title ▶ Author ▶ Year of publication ▶ Publication Date (including dates of other systematic reviews yearly ranges) ▶ Country ▶ Study Settings ▶ Study design (reviews, RCTs, non-RCTs, cluster RCT's, Quasi experimental studies) ▶ Interventions performed. ▶ Study period (MMYYYY to MMYYYY) ▶ Country of study
Population of interest	▶ PLHIV on ART who breast/chest feed their infants. ▶ Infants being breast/chest feed. ▶ Mixed feeding
Population demographics	▶ Number of participants ▶ Length of follow-up. ▶ Amount lost to follow-up/retention/drop-out. ▶ Age of PLHIV ▶ Weaning period ▶ Type of feeding (exclusive breast feeding or mixed feeding) ▶ Preterm birth ▶ Comorbidities (STI, any other)
Exposure types	▶ ART: initiation time, duration, adherence ▶ Person years/months follow-up on ART. ▶ HIV (HIV) viral load testing ▶ Regular viral load testing (4–6 months) ▶ Timing of transmission ▶ PLHIV viral load copies/ml during transmission ▶ Infant frequency of HIV testing and results ▶ Duration of exposure to breast/chest feeding ▶ Weaning period ▶ Type of feeding (exclusive breast feeding or mixed feeding)
Comparators (there might not be a comparator) and outcomes	▶ Risk of HIV transmission from breast/chest feeding with varying viral loads and PLHIV is on ART, categorised by the time period since birth (6 months, more than 6 months) ▶ Risk of HIV transmission per type of feeding (exclusive breast feeding or mix feeding) ▶ Risk of HIV transmission per timing of initiation of ART in the mother

ART, antiretroviral therapy; PICO, population, intervention, comparator, outcomes; PLHIV, person living with HIV; RCT, randomised controlled trial; STI, sexually transmissible infection.

conferences. Furthermore, results of the review could also inform a future systematic review and be of relevance to clinical, healthcare and policy stakeholders.

Contributors PD, HB, CA and AF participated in the conception and design of the study. PD, HB, CA and TE developed the search strategy, tested the feasibility of the study. PD, HB, GB, JD and PVN wrote the manuscript. CA and JM improved the manuscript. All the authors critically reviewed this manuscript and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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