

What are the risks of HIV transmission through breastfeeding?

Primary Reviewer: **Naomi Bulteel**¹, Secondary Reviewer: **Peggy Henderson**²

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¹University of Edinburgh, Scotland

²Child and Adolescent Health and Development (CAH), World Health Organisation, Geneva

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What are the risks of HIV transmission through breast feeding?*

The WHO Pocketbook of Hospital Care for Children estimates the additional risk of mother-to-child transmission (MTCT) of HIV through breastfeeding without interventions to be 5-20%. This risk varies depending on duration and method of breastfeeding, and also because of differences in population characteristics, such as maternal and CD4+ cell counts and RNA viral load.

INTRODUCTION

The human immunodeficiency virus (HIV) pandemic has resulted in a growing number of infants born and living with HIV, with a resultant impact on child welfare and survival, particularly in the developing world. At the end of 2005, there were an estimated 2.3 million children living with HIV globally, 2 million of whom were born in Sub-Saharan Africa [1]. Over 90% of newly acquired infections are attributable to mother-to-child transmission (MTCT), which includes transmission in utero, during labour, and postnatally through breastfeeding [2].

Administration of ARVs perinatally and avoidance of breastfeeding confer similar benefits in terms of risk reduction. Whilst the decreasing global price of ARVs has made regimens more accessible to low-income countries, an unresolved problem is the reduction of transmission through breastfeeding.

METHODOLOGY

The following studies were included: meta-analyses and analytic epidemiological studies, both observational (case control and cohort studies) and interventional (clinical trials) of HIV-infected women and their children; studies performed in general or specific populations and in hospitals or clinics; studies performed in any country. Papers were excluded if they were non-comparative, if their outcomes related to non-clinical endpoints, if they failed to clearly define comparison groups, if they failed to measure outcomes and exposures in the same objective way, if they failed to identify/control for known

confounders and if they were in a language other than English. Methodological quality of included papers was at least type 2b according to the criteria of the Oxford Centre for Evidence-Based Medicine [3].

(http://www.cebm.net/levels_of_evidence.asp)

The exclusion criteria applied left a total of 22 papers for review including 5 meta-analyses, all of which were from the original search strategy.

The primary outcome assessed was the HIV infection status of the child. Participants included HIV infected women and their infants, and risk factors known to be associated with MTCT of HIV were studied, with particular attention to maternal health, breast pathology and infant factors

RESULTS AND DISCUSSION

Rates of breast feeding transmission:

An early meta-analysis by Dunn et al estimated the frequency of breast milk transmission during acute maternal infection at 29% (95% CI, 16-42) and the additional risk of HIV-1 infection in infants who breastfed for at least two years at 14% (95% CI, 7.0-22.0) [4].

A more recent randomised clinical trial from Nairobi found a cumulative probability of HIV-1 infection at 24 months as 36.7% (95% CI, 29.4-44.0) in the breastfeeding arm, and 20.5% (95% CI, 14.0-27.0) in the formula feeding arm [5]. The estimated risk of breast milk transmission was calculated at 16.2% (95% CI, 6.5 – 25.9). These findings are mirrored by a cohort study from Durban, which found an increased risk of 15% (95% CI, 1.8 – 31.8) through breast feeding when compared to formula feeding [6]. Similarly, Fawzi et al found a cumulative incidence for HIV infection of 33.8% (95% CI, 27.5 – 40.1) at 24 months, and a risk of transmission through breastfeeding of 17.9% (95% CI, 11.2-24.5) [7].

The European Collaborative Study found the odds ratio of transmission to be 2.25 (95% CI, 0.97-5.23) in breastfed versus never breastfed children [8]. This is substantiated by a retrospective cohort study from Brazil demonstrating that ever breastfeeding was associated with a 2.2 fold increased risk of infection (95% CI, 1.2-4.2) [9].

Method of feeding

A prospective cohort study in Durban estimated that the probability of HIV detection up to 6 months was similar among never and exclusive breast feeders, at 0.194 (95% CI, 0.136-

0.260) and 0.194 (95% CI, 0.125-0.274), respectively, whilst the probability of transmission in those practising mixed breastfeeding (MF) increased to 0.261 (95% CI, 0.205-0.319). At 15 months, exclusive breastfeeding (EBF) was associated with a 0.247 (95% CI, 0.160-0.344) probability of infection, compared with 0.359 (95% CI, 0.267-0.451) in mixed breast feeders [10]. An earlier analysis of the same cohort demonstrated that the increased probability of infection in infants on mixed feed was statistically significant by 3 months [11].

A study by Iliff et al of a population in Zimbabwe found MF to be associated with a fourfold increase in postnatal transmission at six months when compared to EBF (HR, 4.03; 95% CI, 0.98-16.61; $p=0.05$), and a threefold increase in HIV infection or death (HR, 3.03; 95% CI, 0.95-9.69; $p=0.06$) [12]. The protective effect of EBF decreased over time, but the risk of MF in terms of HIV infection and death were apparent at 18 months (HR, 2.48; 95% CI, 1.26-4.84; $p=0.08$) [12].

In contrast, a cohort study by Magoni et al in Uganda failed to demonstrate a significantly different risk between EBF and MF (hazard ratio for mixed feeding group 1.4; 95% CI, 0.6-3.3; $p=0.4$), although both were associated with an increased risk of transmission when compared with exclusive formula feeding [13]. However, Magoni et al failed to adequately describe the methods used to measure and define early breastfeeding patterns, conceivably admitting an element of maternal recall bias. Moreover, the small sample size means the paper lacked sufficient statistical power to reliably comment on the risk of HIV transmission through breastfeeding intensity. An earlier study by Bobat et al also found no significant increase in risk of HIV-1 transmission through MF [6].

Most recently, an intervention cohort study by Coovadia et al in South Africa found that at 14 weeks of age, infants who received both formula and breast milk were nearly twice as likely to be infected as exclusively breastfed infants (HR, 1.82; 95% CI, 0.98-3.36; $p=0.057$) [14]. Additionally, in a regression analysis with feeding classified as EBF for ≥ 20 weeks, EFF for 6 months, MF starting before 3 months, and MF starting after 3 months, both early mixed feeders (HR, 1.54; 95% CI, 1.10-2.15; $p=0.011$) and late mixed feeders (HR, 1.53; 95% CI, 1.07-2.20; $p=0.021$) were at greater risk of infection than infants receiving EBF [14].

Duration of breastfeeding and timing of postnatal transmission

Nduati and colleagues estimated that 75% of HIV-1 transmission through breastfeeding occurs in the first 6 months, although transmission occurs throughout the duration of exposure [5]. In contrast, a more recent study by Iliff et al found that 68.2% of all postnatal transmission occurred after 6 months [12].

An association between increased duration of breastfeeding, and increased MTCT was reported in a cohort study from Nairobi [15]. Breastfeeding for > 15 months was found to be a significant risk factor for HIV-1 postnatal infection (OR, 23.2; 95% CI, 2.7-211; $p<0.01$). An earlier international pooled analysis by Leroy et al estimated the cumulative probability of late postnatal transmission (from 2.5 months) at 0.7% at 6 months (95% CI, 0.2-2.2), 0.95% at 9 months (95% CI, 0.4-2.4), 2.5% at 12 months (95% CI, 1.3-4.7), 6.3% at 18 months (95% CI, 3.9-9.95), 7.4% at 24 months (95% CI, 4.5-12.1) and 9.2% at 36 months (95% CI, 5.3-15.5) [16]. Iliff et al found a cumulative percentage of postnatal transmission of 3.9% (95% CI, 3.0-4.7), 7.7% (95% CI, 6.6-9.3) and 12.1% (95% CI, 10.5-14.0) at 6, 12 and 18 months respectively.

Miotti et al also demonstrated greater risk with increased duration of breastfeeding, with a cumulative risk of infection from the first month postpartum of 3.5% from 1 to 5 months, 7.0% to 11 months, 8.9% at 17 months and 10.3% at 23 months [17]. A statistically significant decrease in HIV infection rates per person-month occurred through the postpartum period ($p=0.01$), from 0.7% in months 1-5 to 0.2% in months 18-23 [17].

This finding is at odds with the 2004 Breastfeeding and HIV International Transmission Study (BHITS) meta-analysis, which found that the incremental risk of late postnatal transmission did not change significantly with time. The BHITS group found cumulative probability rates from 28 days, of 1.6% at 3 months (95% CI, 0.3-2.9), 4.2% at 6 months (95% CI, 1.8-6.7), 6.0% at 9 months (95% CI, 3.3-8.6), 7.0% at 12 months (95% CI, 4.7-9.3), 7.2% at 15 months (3.6-10.7) and 9.3% at 18 months (3.8-14.8) [18].

Analysis of data collected as part of a randomised trial in Nairobi, showed the overall probability of breast milk transmission of HIV-1 per litre of breast milk to be 0.00064 (95% CI, 0.00035-0.00093). The probability of breast-milk transmission per day of exposure was estimated at 0.00028 (95% CI, 0.00013-0.00042). No significant difference was found between the probability of transmission in children <4 months versus children ≥ 4 months old ($p=0.4$) [19].

Maternal risk factors

- **Maternal plasma HIV and HIV-RNA load**
All studies appraised found a significant increase in risk of HIV-1 transmission with increased plasma HIV-RNA load [7, 20, 21]. A pooled analysis of two short-course ARV trials has shown a 2.65-fold (95% CI, 1.75-4.0) increased risk of transmission for every log₁₀ increase in RNA viral load [22]. Analysis of data from Malawi has shown an association between plasma HIV-1 load and mother-to-child transmission of HIV at both 6 weeks (OR, 3.53; 95% CI, 1.57-7.87) and 12 months (OR, 3.44; 95% CI, 1.56-7.49) of age [23].

- **Maternal breast milk HIV-RNA load**

A secondary analysis of data from the RCT in Nairobi found that first breast milk virus load was a significant predictor of HIV-1 transmission ($p=0.02$) [24]. A 10-fold increase in breast-milk virus load was associated with a 2-fold increase in risk of infection (95% CI, 1.3-3.0; $p<0.01$). Breast-milk viral load was significantly higher in colostrum than in mature breast milk samples collected between weeks 2-48 (2.59 vs. 2.04 log₁₀ HIV-1 RNA copies/mL; $p=0.004$). However, in an analysis of breastfed children in Brazil, a history of colostrum intake was not significantly associated with infant infection ($p=0.95$) [9].

- **Maternal CD4+ count**

The 2004 BHITS meta-analysis showed a strong relationship between maternal CD4+ lymphocyte count at delivery and risk of postnatal transmission of HIV-1: Risk of infection increased eightfold with a CD4+ count of <200 x 10⁶/mL, and 3.5x with a cell count between 200 and 499 x 10⁶/mL [18]. Analyses in Nairobi and Cote d'Ivoire identified the same trend, although blood samples were collected at different stages of the study [15, 20]. Iliff et al demonstrated a sixfold increase in HIV infection at 6 months with a maternal CD4 count at delivery of <200 x 10⁶/mL (HR, 6.23; 95% CI, 3.65-10.23; $p<0.0001$) when compared with a count of ≥ 500 x 10⁶/mL. A CD4 count of <350 x 10⁶ at delivery was associated with a significantly increased risk of HIV infection at 6, 12 and 18 months. Similarly, a recent study by Coovadia et al found that infants born to mothers with

CD4 counts < 200/ μ L were almost four times more likely to acquire HIV or die than those born to mothers with counts > 500/ μ L, when adjusting for confounding variables (HR, 3.97; 95% CI, 2.63-5.98; $p < 0.001$) [14].

This suggests that low maternal CD4+ count is consistently associated with increased risk of transmission through breastfeeding.

• Breast pathology

Semba et al, Embree et al, and John et al demonstrated a statistically significant association with the presence of mastitis and an increased risk of HIV-1 transmission through breastfeeding [15, 21, 23]. John et al found that late maternal mastitis (≥ 2 months) was associated with the highest risk of transmission, whilst Semba et al found the greatest risk at 6 weeks postpartum (OR, 2.38; 95% CI, 1.26-4.42; $p < 0.0008$) [21, 23].

Tess et al found an insignificantly increased risk of HIV-1 transmission if the mother reported bleeding nipples. Cracked nipples were also associated with a minimal, insignificant increased risk of transmission (OR, 0.5; 95% CI, 0.1-4.7) [9]. This is similar to the data from Nairobi, which demonstrated an increased risk of early transmission in the presence of cracked nipples (OR, 2.5) which became significant if the cracked nipples were reported to bleed (OR, 6.5) [21].

A study from Tanzania found that the presence of a maternal breast lesion doubled the risk of postnatal transmission through breastfeeding (RR, 2.0) [7]. This finding is corroborated by associations found by John et al between breast abscesses and late HIV infection (OR, 51.6) [21].

Neither Ekpini et al, Miotti et al, nor Tess et al found a significant relationship between breast pathology and increased risk of HIV-1 transmission, although Tess et al and Ekpini et al showed a trend for increased MTCT in the presence of bleeding or cracked nipples [9,17,25].

Infant risk factors

Infant oral candidiasis has been identified as a risk factor for late postnatal transmission. Embree et al found an increased risk of infection if oral thrush was present before 6 months of age (OR, 7.3; 95% CI, 2.0-27.1, $p < 0.01$) [15]. Ekpini et al also demonstrated this trend, but the increase was not significant (OR, 5.0; 95% CI, 0.6-39.8) [25]. Similarly, John et al showed an insignificant association between infant thrush and overall infection (RR, 1.8; 95% CI, 0.2-13.6) [21].

SUMMARY

The studies analysed found similar rates of additional HIV transmission through breastfeeding, broadly in line with the WHO guideline of 5-20% [26]. Discrepancies between estimates can be explained by variation between studies in methodology, maternal and infant factors, and breastfeeding practices. A standardised model for studies on mother to child transmission (MTCT) has now been developed by the WHO which will facilitate future comparisons [26].

The increase in MTCT associated with breast disease suggests that regular screening is warranted where possible and affordable. Where exclusive formula feeding is not acceptable or feasible, avoidance of breastfeeding during periods of breast pathology could be beneficial. Equally, advice about infant

feeding should include optimal breastfeeding techniques to avoid cracked nipples, milk stasis and mastitis.

The risk of MTCT associated with low maternal CD4+ count and high viral load highlights the need for research into the safety of maternal antiretroviral therapy throughout the breastfeeding period. It is likely that administration of HAART during late pregnancy and lactation would reduce not only MTCT, but also maternal poor health and death associated with disease progression, with additional benefits to the infant. Trials are currently ongoing to assess the safety and efficacy of HAART in this context with follow-up trial data awaited. Evidence on the efficacy of infant prophylaxis is also inconclusive, with more data expected.

At present the WHO advises that unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for infant and mother, exclusive breastfeeding should be practiced. This recommendation is supported by the findings of this review, with the majority of evidence suggesting that practising mixed feeding is associated with a significantly increased risk of MTCT. All HIV-infected mothers should receive counselling, which includes provision of general information about the risks and benefits of various infant feeding options, and specific guidance in selecting the option most likely to be suitable for their situation. Whatever a mother decides, she should be supported in her choice.

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