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A Review of Evidence for Transmission of HIV From Children to Breastfeeding Women and Implications for Prevention

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Abstract

Background—Child-to-breastfeeding woman transmission (CBWT) of HIV occurs when an HIV-infected infant transmits the virus to an HIV-uninfected woman through breastfeeding. Transmission likely occurs as a result of breastfeeding contact during a period of epithelial disruption, such as maternal skin fissures and/or infant stomatitis. Despite extensive epidemiologic and phylogenetic evidence, however, CBWT of HIV continues to be overlooked.

Objective—This article summarizes the available evidence for CBWT from nosocomial outbreaks, during which nosocomially HIV-infected infants transmitted the virus to their mothers through breastfeeding. This article also explores the CBWT risk associated with HIV-infected orphans and their female caretakers, and the lack of guidance regarding CBWT prevention in infant feeding recommendations.

Methods—We searched online databases including PubMed and Science-Direct for English language articles published from January 1975 to January 2011 using the search terms "HIV," "perinatal," "child-to-mother" and "breastfeeding." The citations from all selected articles were reviewed for additional studies.

Results—We identified 5 studies documenting cases of CBWT. Two studies contained data on the number of HIV-infected women, as well as the proportion breastfeeding. Rates of CBWT ranged from 40% to 60% among women reporting breastfeeding after their infants were infected.

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Conclusions—Poor infection control practices, especially in areas of high HIV prevalence, have resulted in pediatric HIV infections and put breast-feeding women at risk for CBWT. Current infant feeding guidelines and HIV prevention messages do not address CBWT, and fail to provide strategies to help women reduce their risk of acquiring HIV during breastfeeding.

Keywords

HIV; perinatal; breastfeeding; transmission

Transmission of HIV from HIV-infected children to their uninfected mothers has been documented on several occasions during hospital-based HIV outbreaks among pediatric patients. ^{1–7} Investigations into these outbreaks implicated the inadequate sterilization of injection equipment and the reuse of supplies for parenteral therapies as the likely sources of pediatric HIV infections. In studies of nosocomially infected children and their mothers, as many as 40–60% of the women who reported breastfeeding after their child's hospitalization were infected with HIV. ^{4,8} Transmission likely occurred when broken skin came into contact with blood during breastfeeding. Although previously considered rare, recent evidence suggests that the risk of HIV transmission from a child to a breastfeeding woman may be underrecognized.

METHODS

References for this review were located through searches of PubMed for English language articles published from January 1975 to January 2011, by use of the terms "HIV," "perinatal," "child to mother" and "breastfeeding," Additional relevant articles published during this period were identified through searches of Google Scholar and ScienceDirect. Reference sections from selected articles were examined for relevant material, and all identified studies were reviewed.

For the 2 studies including information on the number of HIV-infected and uninfected mothers, as well as the proportion of women reporting breastfeeding, odds ratios (ORs) were calculated to determine the odds of HIV infection among mothers who breastfed their infants.^{4,8} The proportion of all HIV-infected women reporting breastfeeding was also calculated. For exposure variables with missing data, a sensitivity analysis was performed that assumed that HIV-infected women with missing breastfeeding data had not breastfed, and that uninfected women with missing data had breastfed.

RESULTS

Evidence for child-to-breastfeeding woman transmission of HIV

Union of Soviet Socialist Republics (USSR)—The first documented cases of child-to-breastfeeding woman transmission (CBWT) were reported in 1988 after nosocomial HIV outbreaks at pediatric hospitals in 3 Soviet cities. A total of 152 children and 12 mothers (8%) were found to be HIV-infected.^{2,8} An epidemiologic investigation established that none of the infected women's sexual partners were HIV-infected, and that all of the infected women had breastfed their infants after the infants' earliest dates of possible infection. Eight of the 12 women (66.7%) had no known risk factors other than breastfeeding their HIV-

infected infants.^{2,7,8} An initial epidemiologic investigation of 41 mother/infant pairs found that 7 (100%) of HIV-infected mothers reported breastfeeding their infants after the earliest possible date of infant HIV infection (mean feeding 4.9 months), compared with 3 (11.5%) HIV-uninfected women (mean feeding 3.8 months).²

An additional study including 123 of the mothers of infected infants discovered that 11 of 18 (61%) women who breastfed their children after their child's admittance to the hospital tested positive for HIV (Table 1). None of the women who had not breastfed their infants were infected. HIV-infected women had significantly greater odds of breastfeeding compared with their uninfected counterparts (OR: 289.8; 95% confidence interval [CI]: 15.5–5412). Of the 8 HIV-infected mothers without other known risk factors, 7 (88%) had infants diagnosed with severe stomatitis that caused bleeding, compared with only 4 (4.0%) infants of seronegative mothers All of the HIV-infected women reported nipple cracks, compared with only 2 of the HIV-uninfected women (OR: 915.4; 95% CI: 41.36–20260). Breastfeeding duration was not a significant risk factor for CBWT in this study.

A molecular epidemiologic study comparing the HIV-1 strains from infants infected during the outbreak with nonoutbreak strains from individuals infected sexually concluded that individuals infected during the outbreak had a common source. Analysis of nucleotide sequences from 1 infant/mother pair found the strains to be closely related to one another and to those strains obtained from other nosocomially infected infants.⁹

Libya—In 1998, 402 children at the Benghazi Children's Hospital were found to be infected with HIV.⁴ An investigation discovered that 20 (5.0%) of their mothers were also infected, though none of the women had a known infected sex partner.^{1,3,5} Three women reported receiving parenteral therapy at the Benghazi Children's Hospital during the outbreak, and 1 woman reported that an area of nonintact skin had come into contact with her child's blood. No additional HIV risk factors were identified among the women. Analysis of blood samples from 15 of the infected children and 14 of their infected mothers indicated a common source of infection for all 29 cases.^{3,5}

Epidemiologic investigations found that the mothers were likely infected by their infants. ^{1,4} After controlling for other possible exposures (sexual or parenteral), breastfeeding during infant hospitalization was a significant predictor of maternal seropositivity (OR: 12.76; 95% CI: 1.38–593). A substudy that included 118 of the mother/child pairs confirmed HIV infection in all 118 infants and 18 mothers, and excluded HIV infection in the remaining mothers and in all 75 of the fathers tested (Table 1). The study also found that 29.9% of uninfected women had reported breastfeeding when the child was first admitted to the hospital, compared with 93.8% of infected women (OR: 35.2; 95% CI: 4.4–282.5). Although the difference was not statistically significant, HIV-infected women reported breastfeeding for an average of 6.5 months after their infant's initial hospital admission, compared with an average of 3.0 months among HIV-uninfected women.

The presence of nipple fissures was also statistically associated with HIV infection in breastfeeding women (OR: 83.0; 95% CI: 8.9–3676.9).⁴ Altogether, 15 (39.5%) of the 38 women who reported breastfeeding after the date of the child's first hospitalization were

HIV-infected.⁴ Fourteen (77.8%) of the 18 HIV-infected women had no known risk factors for HIV other than breastfeeding their infected infant.⁴ When the analysis was repeated to include only mother/infant pairs with a father whose HIV status was known to help control for the possibility of sexually transmitted infection, the relationship between maternal HIV status and breastfeeding remained significant (OR: 12.8; 95% CI: 1.4–593).¹

Kazakhstan—From 2006 to 2007, an outbreak of HIV was identified at 3 children's hospitals in Shymkent, Kazakhstan. One hundred forty-three cases of HIV were identified in previously hospitalized children between the ages of 1 month and 3 years. ¹⁰ An investigation by the Centers for Disease Control and Prevention's Central Asia Region office found that transfusion of blood or blood components, reception of intravenous fluids with an unclean syringe or a hospital stay exceeding 25 days were significantly associated with HIV infection among the infants. ¹⁰

At least 13 (9.1%) of the mothers of these infants were also infected with HIV during the course of the outbreak. ^{10,11} Genetic typing from 5 nosocomially infected infants and their infected mothers revealed a single source of infection. ¹² Given that other risk factors for HIV—including HIV-infected partners or hospital-based exposures—were ruled out, the study concluded that CBWT through breastfeeding had most likely spread HIV from the infants to their mothers. ¹² However, published data from this study did not include the number of women reporting breastfeeding after their child's admission to the hospital.

Kyrgyzstan—Between 2006 and 2007, 86 cases of HIV infection were identified at pediatric hospitals in southern Kyrgyzstan. ¹⁰ Rates of HIV infection were highest among children between the ages of 1 and 2 years. Much like the outbreak in Kazakhstan, inadequate sterilization of injection equipment and the reuse of supplies for the provision of parenteral therapies were implicated in the spread of HIV among hospitalized children. ¹⁰ Reports estimate that at least 16 (18.6%) of the children's mothers were also infected with HIV. Like previous cases of CBWT, breastfeeding was implicated as the most likely route of transmission from infant to mother. Infant mouth sores and maternal nipple lesions were reported by several mothers found to be infected; ^{13,14} however, no published data on the proportion of mothers reporting breastfeeding was available.

Romania—By the end of 1990, the Romanian Ministry of Health had reported 1168 cases of AIDS, mostly from hospitals and orphanages. Thirty-three percent of cases occurred in children 1 year of age, and 94% in children under the age of 13. Although the majority of these children were wards of the state, approximately 38% of cases occurred among nonorphans. A number of cases were believed to have been infected nosocomially, although 57% of children had no known risk factors. ^{15–17}

After locating and testing 493 (45%) of the mothers of infected children, 37 women (8%) were found to be infected with HIV. Eighteen of 30 women (60%) questioned had no known risk factors for HIV infection, including clotting disorders, receipt of a blood transfusion, a history of injection drug use or a sexual contact with an individual infected with HIV/AIDS.

Although no studies were performed to determine the direction of transmission, only 30 of the 74 adult cases of AIDS that had been reported in Romania at this time occurred in women, compared with 1094 pediatric cases. ¹⁵ Given the young age of the pediatric cases and the lack of risk factors among the infected mothers, it is possible that at least some of the women could have been infected by their infants during breastfeeding, rather than the mothers having passed the virus on to their infants perinatally.

Other Settings of Concern

Although published examples of CBWT occurred after pediatric nosocomial HIV outbreaks, transmission is possible in any instance where an HIV-infected child is breastfed by an uninfected woman, including occasions when an HIV-infected child is orphaned and later breastfed by an uninfected female caretaker.

Wet-nursing, the complete nursing of another's infant, still occurs in many parts of the world, although its acceptability varies. Cross-nursing, the occasional nursing of another's infant while the mother continues to nurse her own child, also remains common in many areas. ^{18–20} Estimates on the practices' popularity vary greatly by region, and overall rates remain difficult to determine. Several recent surveys on wet-nursing in the context of HIV have been performed in sub-Saharan Africa. When women were asked whether they would consider using a wet nurse as a breastfeeding alternative for their infants if they themselves were infected with HIV, or would be willing to act as a wet nurse for an HIV-infected friend or family member, rates of acceptability for the practice ranged from less than 37% in Cote d'Ivoire to 74% in Burkina Faso. Acceptability was highest in the context of orphanhood, where women felt that an orphaned baby would ideally be wet-nursed by a female relative. ^{18–20}

Cross-feeding typically occurs on more informal basis than wet-nursing, although research on the topic is limited. A study of 139 women in Gabon found that 40% of those surveyed "breastfed up to four additional infants, other than their own," and that 40% of the infants in the study had been breastfed by as many as 3 women in addition to their biological mothers. In contrast, a population-based survey in South Africa found that 3.5% of women reported breastfeeding a nonbiological child. 23,24

In many African countries, where grandmothers typically bear the responsibility for childcare if a mother is ill or absent, nonpuerperal-induced lactation is sometimes practiced.²⁵ nonpuerperal-induced lactation occurs when lactation (or relactation) is induced through nipple stimulation such as infant suckling. This means that grandmothers and other older female relatives may be at risk for HIV infection if they breastfeed HIV-infected orphans or children in their care.

Especially in high HIV-prevalence areas, these practices may put women or infants at risk for HIV transmission. This is particularly concerning with regard to cross-nursing, which may involve multiple infants and women over long periods of time. Even when knowledge of HIV transmission through breast milk from mother to child is high, women may not be aware of their risk of HIV acquisition from an infected infant while breastfeeding. In cross-

nursing situations, the direction of causation may be difficult to determine, although HIV could potentially be passed from one infected individual to multiple infants and mothers.

The risk for CBWT resulting from HIV-infected orphans is not known, and the number of HIV-infected orphans of breastfeeding age remains difficult to estimate. Worldwide, an estimated 15 million children have lost one or both parents to HIV/AIDS. ^{26–28} In 2003, approximately 3,000,000 children in sub-Saharan Africa were orphaned before the age of 5.^{27,28} It is not known how many of these children were orphaned while they were still breastfeeding, or how many were HIV-infected. Regional estimates from Kenya and Nigeria found that between 36% and 50% of orphaned children under the age of 15 were HIV-infected. ^{29,30} The median age at orphanhood for HIV-infected children in Nigeria was 24.0 months, suggesting that a substantial portion of children were orphaned while they were still young enough to be breastfed. A number of studies have also observed higher rates of maternal mortality among HIV-infected women when compared with their HIV-uninfected counterparts, indicating that HIV-exposed infants are at higher risk of becoming maternal orphans than infants of HIV-uninfected women. ^{31–34}

It remains unclear what proportion of female caretakers choose to breastfeed orphans, or what proportion of cross-feeding or wet-nursing involves HIV-infected orphans. Although cases of CBWT have not yet been documented in this population, the conditions necessary for HIV transmission from child to caretaker are in place.

Current Breastfeeding Recommendations

World Health Organization guidelines on infant feeding make recommendations on breastfeeding by HIV-infected women. The World Health Organization guidelines in 2003 suggested the use of a wet nurse for HIV-infected mothers who chose not to breastfeed their infants.³⁵

These provisions were designed to protect the health of infants, and focused exclusively on the characteristics of the woman agreeing to act as wet nurse. They included guidance on monitoring her HIV status, ensuring her overall health and checking her ability to properly breastfeed the infant in her care.³⁵ The recommendations did not specifically mention testing the HIV status of the infant, although some of these infants will have been perinatally infected with HIV and would have the potential to pass the virus on to uninfected breastfeeding caretakers.

The 2006 HIV and Infant Feeding Update recommended that HIV-infected women should only be counseled thoroughly on infant feeding options such as nursing, expressed milk heat treatment or milk banks if the woman specifically requested additional information on these topics. ³⁶ The technical consultation report from that same year stated that "the group did not come to consensus on removing wet-nursing as an option, but some experts felt wet-nursing should be discouraged. Concerns were raised about risk of transmission from an infected infant to the wet-nurse." ³⁶

The most recent 2010 recommendations make no mention of the practice of wet-nursing, or the risk of HIV transmission to breastfeeding mothers or caregivers from infected infants.

Future recommendations should include guidance on CBWT and the risk of HIV transmission for women who may choose to breastfeed HIV-infected or HIV-status unknown infants.

DISCUSSION

Implications for Prevention

New HIV infections in breastfeeding infants put seronegative women at risk of acquiring HIV. Unfortunately, when CBWT does occur, it may often be overlooked or may be wrongly attributed to mother-to-child transmission, especially in high HIV-prevalence areas. Although significant advances have been made, mother-to-child transmission remains the leading cause of pediatric HIV infection worldwide. Preventing CBWT begins with the elimination of new HIV infections in children, including vertical transmission from mother-to-child, which leads to an estimated 370,000 cases of perinatally acquired HIV each year.³⁷

Other, less common modes of pediatric HIV transmission such as healthcare-associated HIV infections are also of special concern for CBWT. Infection control, proper sterilization and sufficient supplies continue to be a challenge in many healthcare facilities, especially in low-resource settings. Current rates of unsafe injections, transfusion-transmitted infections and nosocomial infections remain unacceptably high, particularly among pediatric patients who are exposed to injections at a greater rate than adults.^{38–41} As malaria incidence—a leading cause of childhood anemia—continues to fall in many parts of the world, the need for pediatric blood transfusions will likely decrease as well. However, in many middle-income and low-income countries, children under the age of 5 remain the most frequently transfused group. Data from Benin, for instance, found that children under the age of 5 received 65% of the estimated 55,000 transfusions performed in the country in 2008.⁴² Only 13% of low-income, and 30% of middle-income countries report having a national blood safety and hemovigilance system in place.⁴²

Although no documented cases have been published to date, cross-feeding or wet-nursing of perinatally HIV-infected infants could put seronegative women at risk for CBWT. Although cross-nursing or wet-nursing may be an alternative feeding strategy for orphaned infants with potential benefits in terms of nutrition and protection from diarrheal diseases, evidence for CBWT demonstrates that the decision by a HIV-negative woman to breastfeed an HIV-infected infant carries substantial risk. If female caretakers are considering breastfeeding HIV-exposed orphans, counseling women on the potential for CBWT and testing both the child and woman for HIV would help make informed feeding decisions and reduce their risk. Additional research and surveillance could better determine the magnitude of risk associated with this practice, and identify instances of CBWT between HIV-infected orphans and their breastfeeding caretakers.

Transmission of an infectious agent from an infant to a breastfeeding caretaker has been documented previously. Syphilis is known to have passed from congenitally infected infants to wet nurses through breastfeeding. ⁴³ Cases of cytomegalovirus transmission from children infected in day-care centers to their mothers through "intimate contact" have also been documented, although the role of breastfeeding has not been specifically explored. ⁴⁴ It is

biologically plausible that other viral agents, such as hepatitis B, are also able to pass from child to mother.

Continued research is needed in countries with high rates of HIV, mother-to-child transmission, orphanhood and wet-nursing or cross-feeding to quantify the prevalence and magnitude of risk associated with CBWT. Policy analysis is needed to weigh the risks and benefits of optimal infant nutrition and the prevention of CBWT. Support should also be continued for programs working to eliminate mother-to-child HIV transmission, which reduce the number of HIV-infected, breastfeeding children and prevent opportunities for CBWT to occur.

Limitations

This article is the first review of HIV transmission from infected infants to breastfeeding women. As such, it is limited by the small amount of published data, and relies heavily on retrospective studies. Case-control studies of CBWT based on mother's self-reported infant feeding modality may be biased as a result.

Published instances of CBWT have documented rates of transmission during breastfeeding as high as 40–60%. Although this risk is substantial, we were unable to calculate the number of women who may be at risk for CBWT globally, or compare this risk with other, better known routes of transmission in women of reproductive age. Data on the transmission of resistant strains is unavailable, and the issue remains an avenue for future research. Finally, this study was limited by a lack of information on pediatric risk factors for CBWT such as viremia, CD4 counts or antiretroviral exposure.

CONCLUSION

While significant gains have been made in reducing global rates of mother-to-child HIV transmission, CBWT has rarely been addressed. The spread of HIV from an infected infant to a mother or caretaker is preventable. Programs to prevent mother-to-child transmission, elimination of unnecessary injections in children, better infection control practices in hospitals, and national blood safety guidelines and hemovigilance systems would likely reduce the number of infants infected with HIV and put fewer breastfeeding women at risk for CBWT. Improved and expanded anti-malaria programs would also reduce the prevalence of severe childhood anemia and lessen the need for pediatric transfusions. Preventing primary infections and providing appropriate, timely treatment for HIV-infected parents can also decrease the number of AIDS orphans and non-biological caretakers, which in turn reduces the opportunities for CBWT to occur. As with other forms of person-to-person HIV transmission, timely diagnoses are the key to preventing further spread. Scaling up early infant HIV testing capacity and access could prevent CBWT by identifying pediatric infections promptly, and providing critical treatment and counseling. Finally, comprehensive infant feeding recommendations and prevention programs should include information about CBWT in order to make women aware of their risks and advise them on the best feeding practices in the context of both maternal and infant HIV infection.

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TABLE 1

Documented Cases of Child-to-breastfeeding Woman Transmission of HIV

Variables	Former USSR ⁴	Sensitivity Analysis*	Libya ⁸	Sensitivity Analysis†
Children included	123	_	118	_
Proportion of mothers included who were HIV-infected	12/123 (9.8%)	_	18/102 (17.6%)	_
HIV-infected women with no known HIV risk factors	8/12 (66.7%)‡	_	14/18 (77.8%) [§]	_
Proportion of HIV-infected women reporting breastfeeding	11/11 (100%)¶	11/12 (91.7%)	15/16 (93.8%)//	15/18 (83.3%)
Proportion of HIV-uninfected women reporting breastfeeding	7/101 (6.9%)**	17/111 (15.3%)	23/77 (29.9%)††	30/84 (35.7%)
Breastfeeding odds ratio (95% CI)	289.8 (15.5–5412)	60.8 (7.4–502.3)	35.2 (4.4–282.5)	9.0 (2.4–33.6)
Proportion of all women reporting breastfeeding who were HIV- infected	11/18 (61.1%)	11/28 (39.3%)	15/38 (39.5%)	15/45 (33.3%)

Includes only studies that reported the proportion of HIV-infected and HIV-uninfected women reporting breastfeeding.

^{*}The sensitivity analysis assumes that the 1 HIV-infected woman with missing data on breastfeeding had not breastfed, whereas all 10 HIV-uninfected women missing infant feeding data had breastfed.

 $^{^{\}dagger}$ The sensitivity analysis assumes the 2 HIV-infected women missing data on breastfeeding had not breastfed, and that all 7 HIV-uninfected women with missing infant feeding data had breastfed.

[‡]Three women reported receiving injections at the same hospital as the infected children. Two women had a seropositive sexual contact.

 $[\]ensuremath{\S{}}$ Four HIV-infected women reported needle sticks or intravenous treatment during the outbreak.

[¶]One HIV-infected woman was missing data on breastfeeding.

^{//}Two HIV-infected women were missing data on breastfeeding.

^{**}Ten HIV-uninfected women were missing data on breastfeeding.

 $^{^{\}dagger\dagger}$ Seven HIV-uninfected women were missing data on breastfeeding.

⁻ indicates data not available.