A Case Series of 104 Women Infected with HIV-1 via Blood Transfusion Postnataally: High Rate of HIV-1 Transmission to Infants through Breast-Feeding

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We investigated transmission of human immunodeficiency virus type 1 (HIV-1) via breast-feeding by 104 Chinese mothers who acquired the infection through blood transfusion postnataally. Of 106 children, 38 (35.8%) were infected. All children survived to age 5 years, and their survival curve was similar to that of their mothers. These findings suggest a high rate of HIV-1 transmission via breast-feeding when mothers were infected postnataally via blood transfusion, perhaps because of the higher viremia expected during the acute phase of infection. The course of disease among infected children was significantly less rapid than that among newborns infected perinatally, suggesting that a brief window of HIV-1–free life often enables the immune system of an infant to stave off rapid disease progression.

Globally, in 2007, nearly 370,000 children were newly infected with human immunodeficiency virus (HIV) type 1 (HIV-1), and 270,000 died of AIDS. More than 90% of children living with the virus acquired the infection from their mother during pregnancy, birth, or breast-feeding. Breast-feeding remains an important channel for vertical transmission of HIV-1, especially in resource-limited settings. Although transmission of HIV-1 through breast-feeding by chronically infected mothers has been well studied, transmission attributable to postnataally acquired maternal infections has not.

The changing face of the HIV-1 epidemic in China has been recently reviewed elsewhere [1]. By October 2007, there were 223,501 reported cases in China, with 27.8% of those infections occurring among women. The Chinese government estimates that there is a total of 700,000 HIV-1–positive persons in China, including 9000 children. As a percentage of all modes of transmission, mother-to-children transmission (MTCT) accounted for 1.6% of cases in 2007 [2]. The factors associated with transmission via breast-feeding in China have not been studied, although breast-feeding is the preferred infant feeding practice in the country, with an estimated prevalence of 97.6% [3]. The present study focuses specifically on MTCT via breast-feeding when mothers acquired HIV-1 through blood transfusion postnataally.

Methods. Although Henan is widely considered to be the epicenter of the bloodborne HIV-1 epidemic in China, this retrospective case series enrolled women from 7 counties in Hubei and from 1 county in Hebei, all of which lie close to the border with Henan. From January 2000 through June 2008, a total of 104 HIV-1–positive mothers and their 106 children were enrolled in this retrospective case series. The enrollment criteria were infection of the mother with HIV-1 as a result of blood transfusions performed because of excessive bleeding during vaginal delivery or cesarean section and exclusive breast-feeding.

Mothers were identified and screened for enrollment in 3 ways. First, hospital records were traced for blood transfusions occurring between 1994 and 1999. A total of 1598 blood recipients were found to be positive for the virus of HIV-1; of these individuals, 367 (23.0%) were found to be HIV-1 positive. Of these individuals, 83 were women who acquired the virus via blood transfusion postnataally. This screening process documented the deaths of 4 mothers who had received blood transfusions from an infected source between 1994 and 1999, as well as the death of 1 child. Although all 5 individuals died of opportunistic infections that were characteristic of AIDS, none had been tested for HIV-1 and therefore were excluded from the study because their infection status could not be determined with certainty. Second, 22 mothers who acquired HIV-1 via blood transfusion postnataally were identified when
they subsequently presented to healthcare facilities with opportunistic infections. Third, 4 mothers were identified as having infection when they underwent testing while receiving antenatal care for a subsequent pregnancy. For these 109 mothers, infection was traced to paid blood donors who had either died of AIDS or were living with HIV-1. Five mothers mixed breast-feeding with formula feeding and thus were excluded from the analysis.

All 104 women who were enrolled and their husbands denied engaging in other high-risk behaviors (ie, previous blood transfusion, blood selling, injection drug use, or unsafe sex). Maternal HIV-1 infection was confirmed by Western blot analysis. Their 106 children, including 2 sets of twins, were exclusively breast-fed. None of the children had a history of blood transfusion. Samples of venous blood were drawn from all children and were tested by enzyme-linked immunosorbent assay (ELISA) for the presence of HIV-1 infection, and samples for which results were positive had their results confirmed by Western blot analysis.

Through face-to-face patient interviews and review of the medical records, information on patient demographic characteristics, the mode of delivery, and the reason for receiving blood transfusion was collected. Infant feeding practices, duration of breast-feeding, and history of mastitis or cracked nipples were determined based on the recall of the mother. Although collecting information retrospectively introduces the possibility of recall bias, we believe that, because most (80 of 104) of these women have only 1 child, their memory of breast-feeding duration and occurrence of breast disease is relatively accurate.

To determine viral subtypes, DNA of the mothers and their HIV-1–infected children was extracted from whole blood, and the p17 region of gag (560 bp) was amplified. The primers and conditions were the same as those described elsewhere [4]. Amplified products were purified and submitted for DNA sequencing. All sequences obtained were first subjected to an HIV-1 BLAST (Basic Local Alignment Search Tool) search, to compare them with related reference sequences. Phylogenetic trees were generated using the neighbor-joining method of Kimura, which is implemented in the Molecular Evolutionary Genetics Analysis (MEGA) software program (version 3.1). The genetic distances between the HIV-1 sequences were calculated using BLAST.

Associated factors for vertical transmission of HIV-1 through breast-feeding were examined using SPSS software (version 13.0; SPSS). Categorical data were analyzed by cross-tabulations. All reported \( P \) values are 2-tailed. Survival of the mothers and their infected children was analyzed using the Kaplan-Meier method.

The study was approved by the research and ethics committee of Zhongnan Hospital at Wuhan University. All mothers provided written informed consent for themselves and for their children, for review of their medical records, interviews, and blood draws.

**Results.** All 104 mothers were infected via blood transfusion after experiencing excessive bleeding during vaginal delivery or cesarean section at 12 healthcare facilities from 1994 through 2000 (figure 1A). Although the central government officially prohibited blood-selling practices by 1995 and passed the Blood Transfusion Law in 1998, infections due to blood transfusion in this cohort were recorded as late as 2000, suggesting that transfused blood was not universally screened several years after the policy was promulgated.

The average maternal age was 34.7 years (range, 31–42 years) at enrollment and 24.4 years (range, 22–30 years) at the time of delivery and blood transfusion. The average age of offspring at investigation was 8.2 years (range, 4–11 years).

Thirty-eight of the 106 enrolled children were HIV-1 positive, for a transmission rate of 35.8% (95% confidence interval [CI], 26.7%–44.9%). The average duration of breast-feeding was 16.5 months (range, 1–28 months). Duration of breast-feeding was not significantly associated with vertical transmission (figure 1B and 1C). Sixteen of 104 mothers were afflicted with mastitis or cracked nipples during lactation with the infant of interest; 10 of their 16 children were HIV-1 positive. Eighty-eight mothers did not recall having any episodes of breast disease; 28 of...
Figure 2. Survival of mothers and children in a case series from central China across time, compared with survival data for a prospective cohort of children exposed to human immunodeficiency virus type 1 in Rwanda [6].

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Their 90 children were HIV-1 positive. Therefore, the presence of breast disease while breast-feeding significantly increased the risk of transmission of HIV-1 from 31.1% (95% CI, 21.5%–40.7%) among those with no history of breast disease to 62.5% (95% CI, 35.4%–84.9%) among those with history of breast disease during the lactation period of interest (P = .016).

Seventeen pairs of mother-child samples of DNA extracted from peripheral blood mononuclear cells were sequenced and analyzed phylogenetically. The HIV-1 sequence found in each infected child was highly related to that found in his or her mother, clearly documenting vertical transmission. All sequences that were identified belonged to subtype B, the dominant HIV-1 strain in the region [5].

Sixteen of the mothers (15.4%; 95% CI, 8.5%–22.3%) and 5 of the children (13.2%; 95% CI, 4.4%–28.2%) died of AIDS-associated diseases before starting antiretroviral therapy (figure 2). All children lived at least to age 5 years. The mean duration of survival before receipt of antiretroviral therapy was 11.8 years for mothers (95% CI, 11.3–12.3 years) and 12.0 years for children (95% CI, 11.2–12.8 years), with no significant difference noted between the 2 groups (P = .555), as evidenced by Kaplan-Meier analysis (figure 2).

Discussion. In 1985, HIV-1 infection in a breast-fed child whose mother had acquired the virus via blood transfusion after cesarean section was first reported [7]. Another study subsequently confirmed that the virus could be transmitted through breast-feeding [8].

This retrospective case series suggests a high rate of vertical transmission (35.8%) via breast-feeding when mothers were infected postnataally via blood transfusion, as compared with
the rate of 9%–16% documented in studies of postnatal vertical transmission by women during chronic infection [9, 10]. In a cohort of 212 mother-infant pairs in Kenya, Nduati et al [10] estimated that the risk of HIV-1 transmission through breast-feeding is 16.2% (95% CI, 6.5%–25.9%) by age 24 months. The Breastfeeding and HIV International Transmission Study Group estimated that the rate of transmission of HIV-1 via breast-feeding is 9.3% at age 18 months [9].

Compared with studies of HIV-1 transmission through breast-feeding by chronically infected women, relatively little is known about HIV-1 transmission through breast-feeding by mothers who were infected in the postnatal period. The few studies that exist are characterized by small sample sizes or single case reports [8]. In 1992, in a meta-analysis of studies examining MTCT through breast-feeding, Dunn et al [11] compared vertical transmission rates between women with postnatal versus prenatal infections. Breast-feeding by women with postnatal infection resulted in a risk of transmission of 29% (95% CI, 16%–42%), whereas breast-feeding by those with prenatal infections resulted in a risk of transmission of 14% (95% CI, 7%–22%). Our rate of 35.8% for postnatally acquired HIV-1 infection in the mother is somewhat higher, but it is in line with this estimate.

The higher rate of transmission may be the result of the greater viremia expected in these women, who were likely to be in the acute phase of infection after receiving contaminated blood. Studies have shown that, during the acute phase of infection, which lasts several days to several weeks, viral loads may be as high as 10^7–10^8 copies/mL, facilitating transmission of HIV-1 [12]. Research has also shown an association between a higher viral load and an increased risk of breast-feeding transmission due to a higher viral load in breast milk [13].

Although other studies have suggested various factors associated with HIV-1 transmission via breast-feeding, the only statistically significant association noted in the present study was the presence of mastitis or cracked nipples during lactation. Mothers who had a history of breast disease had a risk of HIV-1 transmission of 62.5% (95% CI, 35.4–84.9%), compared with women with and without history of breast disease, whose risk of transmission was 31.1% (95% CI, 21.5%–40.7%). This finding is in line with the findings of a previous report [14].

Some studies have suggested an association between prolonged breast-feeding (beyond 15 months of age) and an increased risk of HIV-1 transmission, but our results showed no significant difference in transmission rates according to duration of breast-feeding (figure 1B and 1C) [14]. This finding suggests that much of the transmission may have occurred early, because no statistically significant accumulation of infections was observed beyond 6 months of breast-feeding. Nduati et al [10] estimated that, for their cohort of breast-feeding mothers with preexisting HIV-1 infection, a 63% risk of transmission through breast-feeding occurred by 6 weeks and a 75% risk of transmission occurred by 6 months. The association between the period of acute infection in the mothers and the start of lactation further suggests that transmission likely occurred early.

The course of disease among infected children before treatment became available was quite different from that noted in prior reports of infant survival in the context of MTCT. Previous studies showed that, among infants infected vertically, the mortality rate in the first 2 years of life was 35%–59%, whereas all children in the present cohort survived to age 5 years and had a mortality rate of 13.2% after a mean of 9.1 years, in the absence of antiretroviral therapy [6]. Studies have shown differences in the mortality rates for infants and children <2 years of age who acquired HIV-1 in utero (67.5%), intrapartum (65.1%), or postnatally (33.2%) [15]; however, in our study, the rate was notably lower. A lower mortality rate could potentially be explained by the loss of data on children who died early and therefore were not captured in the study. A specific effort looking into such a possibility identified only 1 child of an HIV-1–exposed mother who died before the study was conducted, but the infection status of mother and child was unknown. Thus, we do not find evidence of enrollment bias. A significantly lower mortality rate among children in this cohort suggests that even a brief window of HIV-1–free life enables the immune system of an infant to develop and stave off rapid disease progression in most cases. Such a profound conclusion warrants follow-up studies.

To our knowledge, the present study is the first study in China to report HIV-1 transmission via breast-feeding by women who acquired HIV-1 postnatally. Although this case series documents the tragedy in Hubei and Hebei, it is possible that the situation in Henan may be even more dire. The circumstances that led to these infections in central China were a unique tragedy that occurred in a particular historical and socioeconomic context. One broad lesson is the importance of ensuring that policies promulgated at national or provincial levels are accompanied by concrete local plans to ensure that the gap in time between the promulgation and implementation of policies is minimized. We hope never to see such a case series again.

References


