

Articles

International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection

Valérie Leroy, Marie-Louise Newell, Francois Dabis, Catherine Peckham, Philippe Van de Perre, Marc Bulterys, Christian Kind, R J Simonds, Stefan Wiktor, Philippe Msellati, for the Ghent International Working Group on Mother-to-Child Transmission of HIV

Summary

Background An understanding of the risk and timing of mother-to-child transmission of HIV-1 in the postnatal period is important for the development of public-health strategies. We aimed to estimate the rate and timing of late postnatal transmission of HIV-1.

Methods We did an international multicentre pooled analysis of individual data from prospective cohort studies of children followed-up from birth born to HIV-1-infected mothers. We enrolled all uninfected children confirmed by HIV-1-DNA PCR, HIV-1 serology, or both. Late postnatal transmission was taken to have occurred if a child later became infected. We calculated duration of follow-up for non-infected children from the time of negative diagnosis to the date of the last laboratory follow-up, or for infected children to the mid-point between the date of last negative and first positive results. We stratified the analysis for breastfeeding.

Findings Less than 5% of the 2807 children in four studies from industrialised countries (USA, Switzerland, France, and Europe) were breastfed and no HIV-1 infection was diagnosed. By contrast, late postnatal transmission occurred in 49 (5%) of 902 children in four cohorts from developing countries, in which breastfeeding was the norm (Rwanda [Butare and Kigali], Ivory Coast, Kenya), with an overall estimated risk of 3.2 per 100 child-years of breastfeeding follow-up (95% CI 3.1–3.8), with similar estimates in individual studies ($p=0.10$). Exact information on timing of infection and duration of breastfeeding was available for 20 of the 49 children with late postnatal transmission. We took transmission to have occurred midway between last negative and first positive HIV-1 tests. If breastfeeding had stopped at age 4 months transmission would have occurred in no infants, and in three if it had stopped at 6 months.

Interpretation Risk of late postnatal transmission is consistently shown to be substantial for breastfed children born to HIV-1-positive mothers. This risk should be balanced

against the effect of early weaning on infant mortality and morbidity and maternal fertility.

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Introduction

Mother-to-child transmission of HIV-1 infection can occur during pregnancy in the intrapartum period or postnatally.¹ HIV-1 DNA is present in breastmilk² and postnatal transmission can occur through breastfeeding.^{3,4} Breastfed children have a higher risk of mother-to-child transmission than those who have never been breastfed,⁵ and prospective follow-up of children born to HIV-1-infected mothers has shown that some infants become infected postnatally after loss of maternal antibodies.^{6,7}

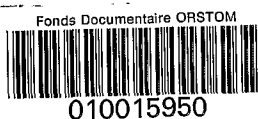
Avoidance of breastfeeding by HIV-1-infected women is recommended if safe and affordable alternatives are available,⁸ a practice reinforced by WHO, UNICEF, and UNAIDS (UNAIDS website [HIV and infant feeding <http://coww.unaids.org/unaids/document/epidemic/infant.html>] accessed on July 28, 1998). In many developing countries, however, high expense and rates of infant morbidity and mortality are associated with alternative feeding methods and identification of HIV-1-infected pregnant women. In places where the prevalence of HIV-1 is high, postnatal acquisition of HIV-1 infection through breastfeeding remains a concern and a possible compromise would be to stop breastfeeding early.^{8–10}

Although breastfeeding has been estimated to double the risk of vertical transmission,⁴ the exact risk and timing of transmission attributable to breastfeeding remain unclear. A randomised controlled trial of breastfeeding compared with bottle feeding is underway in Nairobi, Kenya,² which should provide a reliable estimate of the additional risk of HIV-1 transmission attributable to breastfeeding. The postnatal transmission risk of HIV-1 can also be assessed in large prospective studies with frequent laboratory follow-up of children born to HIV-1-infected mothers, in which postnatal transmission can be distinguished from intrapartum transmission.¹¹ In such studies, late seroconversions in breastfed children have been reported,^{6,7,12–15} but the reliability of risk estimates needs to be improved.

Improved understanding of the risk and timing of postnatal transmission of HIV-1 is important for the development of strategies for infant-feeding and weaning policies.^{9,16} Such understanding is especially relevant to interventions to decrease vertical transmission that are currently being developed and assessed.^{17,18} We did an international multicentre pooled analysis to estimate the rate and timing of late postnatal transmission of HIV-1.

Unité INSERM 330, Université Victor Segalen Bordeaux 2, 146 rue Léo-Saignat, 33076 Bordeaux, France (V Leroy MD, Prof F Dabis MD), Institute of Child Health, Guildford Street, London, UK (M-L Newell MD, Prof C Peckham MD), Centre Muraz, Bobo-Dioulasso, Burkina Faso (Prof P Van de Perre MD); Centers for Disease Control and Prevention, Atlanta, Georgia, USA (M Bulterys MD, R J Simonds MD); Swiss perinatal cohort, Kantonspital, St Gallen, Switzerland (C Kind MD); Projet RETRO-CI, Abidjan, Côte d'Ivoire (S Wiktor MD); and Programme SIDA, ORSTOM, Abidjan (P Msellati MD)

Correspondence to: Dr Valérie Leroy (e-mail: valeriane.leroy@dim.u-bordeaux2.fr)



Study site	Laboratory follow-up†	Number of children born to HIV-1-infected mothers	Breastfed (%)
Abidjan, Ivory Coast: Retro-CI ¹⁴	WB ELISA PCR	188	100
Butare, Rwanda ¹²	WB ELISA P24	254	99
Kigali, Rwanda ²¹	WB ELISA PCR	218	98
Nairobi, Kenya ^{23*}	WB ELISA PCR	743	100
Europe, European Collaborative Study ²⁵	WB ELISA PCR VC	1954	3
France, French Cohort Study ^{26*}	WB ELISA PCR VC	729	2
Switzerland, Swiss Study ²⁷	WB ELISA PCR VC P24	363	5
USA, PACT Study ²⁸	WB ELISA PCR VC P24	1548	1

*Summary data only. †WB=western blot. VC=viral culture; P24=P24 antigenaemia.

Table 1: Characteristics of the eight included studies

Methods

We gathered all published and unpublished data from completed or continuing cohort studies, in which information was available on sequential prospective laboratory follow-up (PCR, ELISA, and western blot) of children born to mothers known to be infected with HIV-1 before or at delivery. To limit the publication bias inherent to pooled analysis,¹⁹ we contacted all potential investigators through the International Working Group on Mother-To-Child Transmission of HIV-1, a large network of researchers in developing countries.^{17,20} All children followed up from birth were eligible. We requested individual data, but if these were not available, we accepted summary data. For each child, we collected information on maternal serological HIV-1 status at delivery, date of birth, date of last follow-up, HIV-1-infection status and mortality, duration of breastfeeding, and all laboratory results for diagnosis of the child's HIV-1 infection, with corresponding dates.

We defined each child's HIV-1 status according to an algorithm with serological or DNA-PCR criteria, or both, following the Ghent classification.^{17,20} We took uninfected children to be those with negative PCR results after age 2.5 months, confirmed by negative western blot after 9 months, or negative ELISA at 18 months or older, or children in the absence of a PCR test result who had lost maternal antibodies.^{17,20} We classified children as having HIV-1 infection if: they had a positive PCR at any age,

confirmed by a subsequent positive PCR, a positive western blot at age 15 months or later, or a positive ELISA at or after age 18 months; or they had only a positive antibody test, as defined previously. We excluded children with inconclusive results. Among HIV-1-infected children, we classified acquisition of HIV-1 infection as having occurred in utero, intrapartum, or early postnatally if PCR was positive before age 2.5 months.²¹ We classified late postnatal transmission as HIV-1 infection that was diagnosed after age 2.5 months in children with laboratory evidence of no infection at or after age 2.5 months. We could not assess timing of HIV-1 infection in children who were persistently HIV-1-antibody positive without PCR assessment. Because viral culture was not routine, we did not use this method in the algorithm to define cases of late postnatal transmission.

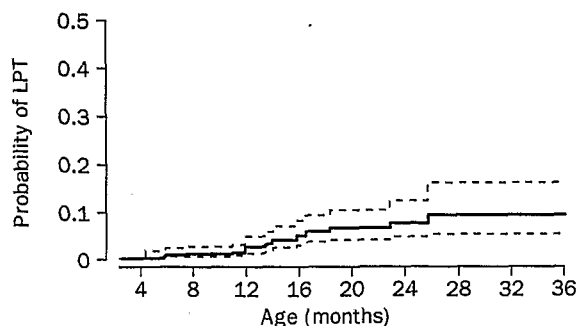
We based the denominator for the estimation of the rate of late postnatal transmission on children with documented absence of infection after age 2.5 months. We chose the cut-off time of 2.5 months because a negative DNA PCR early in life in breastfed infants does not necessarily imply no infection and early postnatal and intrapartum infection cannot be distinguished. This time also allowed for the time of testing in the studies and kept to a maximum the number of children with test results. We took date of entry in the study as the date of the first negative HIV-1 test.

We defined all time-points in the analysis in relation to laboratory assessments. We took the start of the period during which infants were at risk of late postnatal transmission to be the age at which children were diagnosed as being uninfected. Our endpoint was the age at the last laboratory test in children who remained uninfected, or the midpoint between the date of the last negative and the first positive test in children who became infected. For breastfed children, we calculated the start of the breastfeeding period from the first negative HIV-1 test. We extended the contribution of the breastfeeding period to the risk of late postnatal transmission to 2 months after breastfeeding stopped to allow for the occurrence of seroconversion.

We first calculated the rate of infection for each study individually and then for pooled studies, as: (number of cases of late postnatal transmission/[number of children followed×years from the time of diagnosis of absence of infection])*100. We

Study site	Number of children in our study	Median follow-up in months (range)	Number of child-months of follow-up	Number of late postnatal transmission cases	Risk of late postnatal transmission in child-years (95% CI)
Abidjan, Ivory Coast					
Total	114	22 (1.5-45.4)	2575	6	0.028 (0.027-0.046)
Breastfed		12 (1.5-25.4)	1273	6	0.057 (0.055-0.082)
Non-breastfed		14 (1.4-36.3)	1302	0	0
Butare, Rwanda					
Total	183	7.4 (1.0-15.6)	1350	7	0.062 (0.060-0.087)
Breastfed		7.2 (0.7-14.7)	1269	7	0.066 (0.064-0.092)
Non-breastfed		5.4 (1.3-11.9)	81	0	0
Kigali, Rwanda					
Total	152	22 (0.03-39.0)	3408	7	0.025 (0.024-0.041)
Breastfed		16 (0.1-33.0)	2325	7	0.036 (0.035-0.055)
Non-breastfed		11 (0.03-33.0)	1083	0	0
Nairobi, Kenya					
Breastfed	453	..	13 617	29	0.026 (0.025-0.034)
Europe					
Total	902	30.6 (0.1-122.0)	27 560	0	0
Breastfed		0.34	1	0	0
Non-breastfed		30.6 (0.1-122.0)	27 560	0	0
France					
Total	724	..	9762	0	0
Breastfed			142	0	0
Non-breastfed			9620	0	0
Switzerland					
Total	254	18.4 (1.7-72.0)	4718	0	0
Breastfed		7.3	7	0	0
Non-breastfed		18.4 (1.7-72.0)	4711	0	0
USA					
Total	924	22.2 (0.03-103.0)	20 528	0	0
Breastfed		1.1	1	0	0
Non-breastfed		22.2 (0.03-103.0)	20 527	0	0

Table 2: Estimated risk of late postnatal transmission from eight included studies by breastfeeding practice



Cumulative probability of late postnatal transmission of HIV-1 among breastfed children with estimation of the timing of infection

Kaplan-Meier method with delayed entry ($n=20$ of 429). Dotted lines represent 95% CI

estimated this rate separately for breastfed and non-breastfed periods. Rates are presented with 95% CIs. We tested for homogeneity between the different estimates of late postnatal transmission with Poisson regression.²² Among breastfed children with individual information on timing of infection, not summary information, we did a survival analysis to estimate the cumulative probability of having late postnatal transmission by the Kaplan-Meier method with delayed entry (entry time defined as time of diagnosis of absence of infection for each child). We used this method to allow for the truncation at entry in the late postnatal transmission study.²³ We attempted to collect information on possible determinants of late postnatal transmission among breastfed children, such as maternal age, maternal CD4 count, maternal clinical status, and history of breastfeeding, but such information was not generally available and we could not investigate the role of risk factors.

Results

By October, 1997, we had gathered individual data from six cohort studies, and summary data from two other studies, including 5997 children (table 1^{7,12,14,24-28}). In the four cohorts from industrialised countries, 5% or less of children were ever breastfed, and laboratory follow-up included HIV-1 serology, DNA PCR, and viral culture every 3 months after birth. In the four developing-country cohorts, breastfeeding was the norm and, with the exception of Butare where only serology was available, HIV-1-antibody and DNA PCR tests were done regularly from age 3 months.

Table 2 shows for each study the number of children enrolled in our study, with duration of follow-up from time of non-infection, and the number of cases of late postnatal transmission stratified by breastfeeding. Overall, we enrolled 2804 children from industrialised countries and 902 from developing countries. Median follow-up after first negative HIV-1 result ranged from 7.4 months (Butare) to 30.6 months (Europe).

No case of late postnatal transmission was diagnosed in non-breastfed children. During the total period of breastfeeding, 49 children with late postnatal transmission were detected, giving an overall estimated risk of late postnatal transmission of 3.2 per 100 child-years of breastfeeding follow-up (95% CI 3.1-3.8); estimates in individual studies ranged from 2.6% to 6.6% per 100 child-years of breastfeeding follow-up and were consistent ($p=0.10$).

429 children, including 20 of the 49 children with late postnatal transmission, had information about timing of acquisition of HIV-1 infection (figure). The median age at which these children had had a negative test result was 5.8 months (range 2.5-15.7), with no significant difference

between those who became HIV-1 positive and those who remained negative ($p=0.36$). Median length of breastfeeding exposure was 15.5 months (3-36). The cumulative probability of acquisition of late postnatal transmission was 0.7% at age 6 months (0.2-2.2), 0.95% at 9 months (0.4-2.5), 2.5% at 12 months (1.3-4.7), 6.3% at 18 months (3.9-9.95), 7.4% at 24 months (4.5-12.1), and 9.2% at 36 months (5.3-15.5).

Therefore, none of the 20 children with late postnatal transmission would have been infected if breastfeeding had stopped at age 4 months, and only three would have been infected if breastfeeding had stopped at age 6 months. We took the time of infection to be midway between time of last negative and first positive test. Since we may have overestimated the benefit of early discontinuation of breastfeeding, we repeated the analysis with a worst case scenario, in which we took infection to have occurred immediately after the last negative test. Two of the 20 children would have been infected if breastfeeding had been discontinued at age 4 months, and four if breastfeeding had ceased at 6 months.

Discussion

The previously reported risks of late postnatal transmission of HIV-1 infection were based on small numbers and ranged from 5% to 12%,^{11,14} or a yearly incidence of 5.8 per 100 child-years of breastfeeding.¹² A study in Nairobi, Kenya, reported 40 cases of acquisition of infection though breastfeeding in children of mothers with either prevalent or incident HIV-1 infection.²⁴ We attempted to overcome difficulties of differences in definition of late postnatal transmission, laboratory methods for assessment of late postnatal transmission, and duration of follow-up by the pooling of individual data from eight prospective cohort studies and applying a standard definition of infection. Because these individual studies had different laboratory follow-up methods and timing for HIV-1 diagnosis heterogeneity was introduced, but the variability between studies was not significant. Since the estimation of paediatric HIV-1 infection rate was the primary objective of all these studies, we limited potential information bias by handling the most relevant data in our pooled analysis.¹⁹ Four eligible prospective studies that we did not include reported estimates of late postnatal transmission that ranged from 4% (eight of 189) after age 5 months in Kinshasa, Zaire,¹³ 15% (eight of 53) after age 6 months in Soweto, South Africa,⁷ 4% (three of 73) after age 12 months in Brazzaville, Congo,²⁹ and an incidence of 6.2 per 100 child-years of breastfeeding after age 6 months in Dar es Salaam, Tanzania.¹⁵ Although with different definitions of late postnatal transmission and methods for clinical and laboratory follow-up, these rates were difficult to compare directly, they were similar to our findings. The similarity between individual studies in our analysis, which used common definitions, strengthened the reliability of the overall estimate.

Although postnatal transmission can occur when mothers acquire HIV-1 infection during lactation,^{3,4} transmission is most common from mothers who are infected at the time of delivery. Study of postnatal transmission of HIV-1 infection among seroconverting mothers was not our objective since the risk of late postnatal transmission differs from that for seropositive women at delivery.

Although substantial, the incidence of 3.2 per 100 child-years of breastfeeding for late postnatal transmission

underestimates infection occurring through breastfeeding, since infections acquired before age 2.5 months would have been excluded. The contribution of this additional risk of 3.2 for infection after age 2.5 months to an overall rate of about 25% in mother-to-child transmission in breastfeeding populations is about 14%. This finding could have important implications for interventions to prevent peripartum infection.^{1,18} Before implementation of any intervention programme to decrease mother-to-child transmission around the time of birth in breastfeeding populations, however, the subsequent risk of acquisition of infection through breastfeeding should be considered. Intervention trials will need to have sufficiently long follow-up to fully estimate this risk.

There is a need to find out how best to advise HIV-1-infected women in developing countries about the risk of transmission through breastfeeding. Not only is advice important in the initial decision about whether or not to breastfeed, but also in counselling about continuation of breastfeeding after an infant is shown to be uninfected. Information on the timing of postnatal transmission will guide policies on infant feeding and the stopping of breastfeeding in countries with high HIV-1 prevalence in which safe and affordable alternative options are unavailable. Although the advantages of breastfeeding in the absence of HIV-1 infection, have been well documented,³⁰ the risk of acquisition of HIV-1 through long-term breastfeeding may outweigh its benefits in populations with high HIV-1 prevalences, even when childhood mortality rates are high.^{30,31} The stopping of breastfeeding at 6 months is already being considered in the Ivory Coast for HIV-1-infected women,^{14,32} and if implemented, will need to be carefully monitored.³³ Further information is required on the net effect of artificial feeding or the early stopping of breastfeeding on growth, infant morbidity and mortality, and maternal fertility in the context of high HIV-1 prevalence among women and children.

Contributors

Valeriane Leroy, Marie-Louise Newell, and Francois Dabis designed the study, did the analysis, and wrote the paper. Catherine Peckham and Philippe Van De Perre, as members of the Ghent Working Group steering committee, contributed to the design of the study and were involved in the preparation of the manuscript. Marc Bulterys, Christian Kind, R J Simonds, Stefan Wiktor, and Philippe Msellati contributed data, and had substantial input into the writing of the paper.

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