Mother-to-child transmission of HIV-1 in Congo, central Africa

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Objective: To assess the risk of mother-to-child transmission of HIV-1 in a central African population and to study maternal factors associated with perinatal transmission.

Design: Prospective cohort study of infants born to HIV-1-positive women and controls born to HIV-1-negative women enrolled sequentially in two prenatal clinics and one maternity hospital in Brazzaville, Congo.

Subjects and methods: A total of 118 exposed and 208 control infants were followed from birth for at least 2 years. Assessment of infection in children and computation of transmission rate were made according to the European Economic Community/World Health Organization Ghent guidelines (1992).

Results: The transmission rate was 40.4% [95% confidence interval (CI), 30.7–50.1]. Maternal age, parity, history of adverse pregnancy outcome or history of deceased children were not associated with transmission. However, independently, women whose relationship with their infant's father was less than 1 year, or women who had symptoms of HIV-1 during pregnancy had an increased risk of transmission [adjusted odds ratios, 11.1 (95% CI, 2.4–50.2) and 10.3 (95% CI, 2.9–37.1), respectively].

Conclusion: The transmission rate observed in Congo is in the upper range of the rates reported in Africa. The uneven distribution of cofactors for perinatal transmission, such as the presence of symptoms of HIV disease during pregnancy, may explain some of the variation observed across studies.

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[For editorial comment, see pp 1495–1497]

Introduction

The most conservative estimates of the World Health Organization (WHO) indicated that by the end of 1992, more than 5 million women worldwide had been infected with HIV. About 80% of these women, approximately 4 million, were from Africa [1]. Although much research has been conducted since 1982, when pediatric AIDS cases were first reported in North America and Europe [2], much uncertainty still exists about the actual risks of perinatal transmission and the processes involved [3].

Published rates of perinatal transmission vary widely from 13 to 45% [4–13]. Direct comparison of one study with another is difficult, however, because of differ-

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ences in study design, infant HIV infection criteria, and methodology for calculating the risk of transmission. To render study results comparable, investigators involved in HIV-1 perinatal transmission cohort studies in Africa, Europe and North America developed a common methodology for assessing HIV infection in infants and the computation of transmission rates (European Economic Community/WHO Ghent, Belgium, 1992) [14]. Here we report the results of the Congolese cohort study, using this standardized approach.

Methods

Pregnant women who had agreed to participate were screened for HIV-1 antibodies over two periods, May 1987 to March 1988, and August to November 1989. After verbal consent, they were sequentially recruited either during their first prenatal visit or at delivery in three health centers serving Brazzaville's eastern districts.

Women were eligible for inclusion in the cohort with their infants if they were living in the districts served by the participating centers and had given birth to a live-born infant. During the first inclusion period, enrolled HIV-1-positive mothers were matched by age, district of residence and presumed date of delivery with two HIV-1-negative control mothers [15]. During the second inclusion period, HIV-1-positive mothers were matched by age and district of residence with one HIV-1-negative control mother who had delivered on the same or the following day.

Mothers' sera were tested for antibodies to HIV-1 by enzyme-linked immunosorbent assay (ELISA; Diagnostics Pasteur, Marnes-la-Coquette, France). Positive ELISA tests were confirmed by Western blot (Du Pont de Nemours, Rockville, Maryland, USA). Sera were considered positive if they showed antibodies against at least two envelope glycoproteins. All positive results were reconfirmed with a subsequent blood sample.

All women were given their test results and received counseling. At inclusion, they had a physical examination and a basic interview for demographic data and medical and reproductive history. They were then seen monthly with their infant by a medical assistant. Every 3 months, the infants received a standardized physical examination, always by the same pediatrician, and a blood sample was drawn. A nurse maintained continuous contact with the families. Women and/or children who had not been seen during two subsequent monthly visits were actively followed-up. All infants were breastfed.

All available clinical information and laboratory results for mothers and children were reviewed independently by two physicians. Women were classified as symptomatic if they presented with at least one of the WHO clinical AIDS definition criteria [16]. Each infant's HIV status was determined at follow-up. A positive serological test for HIV antibodies at 15 months was considered decisive evidence of HIV infection. Infants who died prior to 15 months were classified as infected if they either had AIDS according to the WHO case definition [16], or met the EEC/WHO Ghent workshop criteria for HIV-related death [14]. Infants who died during the neonatal period, were lost to follow-up, or could not be classified clinically were considered indeterminate.

The rate of transmission was calculated by the direct method based on the case-by-case analysis of the outcome for all children born to HIV-1-positive mothers. An indirect transmission rate was also calculated based on the assumption that, from birth to 15 months, the mortality difference between children born to HIV-1-positive mothers and controls was due to HIV infection. This indirect rate was obtained by combining the mortality difference with the proportion of seropositive children among those who survived to 15 months [14].

The Pearson χ^2 test and the Cochran–Armitage test for linear trend were used to evaluate associations for categorical variables. The probabilities of death at 15 months and their 95% confidence intervals (CI) were calculated using the Kaplan–Meier and Greenwood methods. Adjusted odds ratios were obtained by the logistic regression method. For variables involving more than two levels, distinct dichotomous variables corresponding to each level were entered into the model.

Results

HIV status of children born to HIV-1-positive mothers

A total of 114 HIV-1-positive women and their 118 infants were enrolled in the cohort study. Five mothers had twins, including one stillborn child. Seventy-three children could be tested for antibodies to HIV at 15 months. Fifty-six had seroreverted. Three infants who were seronegative at 12 and 15 months later seroconverted. In computing the rate of perinatal transmission, these three children were considered uninfected. Seventeen children were seropositive at 15 months. Thirty-three children died before 15 months, of whom eight had AIDS. Of the remaining 25, 15 were considered infected because they met the criteria of HIV-related death and 10 could not be classified (Table 1). Finally, of the 12 children who could not be followed-up until 15 months, three were considered uninfected because they had seroreverted at 12 months and the HIV status of the nine other children remained indeterminate.

Of the nine liveborn twins of HIV-1-positive mothers, two pairs were concordant and infected and one pair was concordant and not infected. The HIV status of the three others twins, who were premature and died during their first week of life, was considered indeterminate.

Infants at birth and survival

Infants born to HIV-1-positive mothers were followed from birth along with 208 infants born to 208 HIV-

Table 1. Circumstances of death among the 25 children who did not meet the World Health Organization (WHO) AIDS definition criteria.

	Infant identification number																								
	1†	2†	3†	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
HIV signs and symptoms*																									
Persistent diarrhea (>15 days)							*	*								*				*		*			
Oral candidiasis‡								*					*	*	*		*	*		*			*		
Generalized lymphadenopathy													*		*					*			*	*	
Failure to thrive§							*	*		*	*			*	*			*			*	*			*
Recurrent pneumonia											*										*				*
Circumstances of death																									
Severe infection								*	*		*	*	*	*	*	*	*		*	*	*		*	*	*
Persistent diarrhea							*	*										*				*			
Prematurity	*	*	*	*	*																				
Unknown						*				*															
Age at death (weeks)	1	1	1	1	1	7	7	10	11	11	15	16	16	16	18	20	21	25	26	29	33	41	42	47	54
HIV infection status¶	?	?	?	?	?	?	+	+	?	?	+	?	+	+	+	+	+	+	?	+	+	+	+	+	+

*HIV-related signs and symptoms according to the WHO/European Economic Community Ghent workshop [14]. †Twins; ‡beyond the neonatal period; §no weight gain for a period of 3 months or crossing two percentile lines on the growth chart; ¶assigned based on the presence of HIV-related signs and symptoms, and circumstances of death [14]. ?, indeterminate HIV status; +, HIV-positive.

Table 2. HIV transmission rate among HIV-1-positive mothers according to maternal characteristics.

Maternal characteristics	n	% Transmitting*	*P*
Age (years)			
<21	22	31.8	
21–30	65	46.2	
>30	12	25.0	0.25
Marital status			
Married	42	28.6	
Not married	57	49.1	0.039
Duration of relationship (years)			
<1	32	50.0	
1–5	45	40.0	
>5	22	27.3	0.25
Parity			
1	26	42.3	
>1	73	39.7	0.82
History of abortion			
Yes	22	45.4	
No	77	39.0	0.58
History of miscarriage			
Yes	20	35.0	
No	79	41.8	0.58
History of stillbirth			
Yes	3	33.3	
No	96	40.6	0.80
History of deceased children			
Yes	30	50.0	
No	69	36.2	0.20
HIV-1-related symptoms			
None	53	22.6	
At delivery	23	60.9	
Postpartum	23	60.9	0.001
History of transfusion and/or hospitalization since 1980			
Yes	32	56.3	
No	67	32.8	0.026

*Rate calculated by the direct method (see Methods).

1-negative control mothers. Infants born to HIV-1-positive mothers had a lower birth weight and were more likely to be premature. Their mean birth weight was 2.87 kg compared with 3.08 kg for control infants ($P=0.0004$) and 17.9% had a gestational age less than 38 weeks compared with 7.7% of the control infants ($P=0.005$). After twins were excluded, lower mean birth weight remained the only significant difference between the two groups (2.94 versus 3.08 kg; $P=0.01$).

Probabilities of death in the two groups differed significantly as early as 3 months of age. Survival in infants born to HIV-positive mothers was 0.91 (95% CI, 0.85–0.95) at 3 months, 0.74 (95% CI, 0.66–0.82) at 12 months and 0.71 (95% CI, 0.61–0.79) at 15 months of age. In control infants, it was 0.99 (95% CI, 0.96–1.0) at 3 months, 0.96 (95% CI, 0.92–0.98) at 12 months and 0.95 (95% CI, 0.91–0.97) at 15 months.

Transmission rates

By the direct method, the estimated transmission rate was 40.4% (95% CI, 30.7–50.1). The upper and lower estimates of risk of transmission, assuming that all indeterminate infants were either infected or uninfected, were 33.9% (95% CI, 25.4–42.4) and 50.0% (95% CI, 41.0–59.0), respectively. The indirect transmission rate was 42.7% (95% CI, 32.7–52.7).

Since twinning only occurred among HIV-1-positive mothers and three of the five deaths associated with prematurity occurred in twins, we also calculated the rates of transmission after excluding twins. Point estimates were slightly lower 38.7% (95% CI, 28.1–48.0) by the direct method with upper and lower limits of 47.2% (95% CI, 37.8–56.6) and 32.4% (95% CI, 23.6–41.2), respectively. The indirect estimate was 39.9% (95% CI, 29.5–50.2).

Maternal characteristics and transmission

The sociodemographic characteristics, reproductive history and clinical status of the 99 mothers whose infant's HIV status was known were analyzed for their association with perinatal transmission (Table 2). While age was

Table 3. Logistic regression model of maternal characteristics associated with HIV-1 transmission.

Maternal risk factor	Adjusted OR	95% CI	P
Age (years)			
<21	0.35	0.10–1.17	0.091
21–30	1	-	-
>30	0.56	0.11–2.68	0.448
Duration of relationship (years)			
<1*	10.99	2.40–50.22	0.03
1–5	4.71	1.23–18.03	0.026
>5	1	-	-
Symptoms			
None	1	-	-
Symptoms at delivery	10.33	2.87–37.13	0.001
Symptoms postpartum	8.29	2.38–28.93	0.001

*When women's marital status was put into the model in place of duration of relationship, it was significantly associated with transmission [relative risk, 0.38; 95% confidence interval (CI), 0.15–0.97; $P=0.046$], and the coefficients were only slightly modified. OR, odds ratio.

not associated with transmission, unmarried women and women whose relationship with their infant's father had lasted less than 1 year were more likely to transmit the virus to their infants. At delivery, one mother had AIDS and 23 had symptoms of HIV infection. Twenty-three additional women developed symptoms during the 2-year postpartum period. There was a 2.7-fold increase in the rate of transmission among women who were or became symptomatic compared with those who remained symptom-free. Finally, women who reported at least one hospitalization and/or transfusion since 1980 were also more likely to transmit the virus to their infants. In the multivariate analysis, both the mother's clinical status and her relationship with the infant's father remained independently associated with perinatal transmission (Table 3).

Discussion

Nearly all women in Brazzaville receive prenatal care in specialized mother-child clinics and deliver in one of the city's five maternity hospitals. Our study was conducted in three of these major facilities. Since most women attending the clinics agreed to be tested for HIV and to participate in the study, it is unlikely that the women were selected based on their health status or expectation of access to care. Therefore, we believe the HIV transmission rate reported here accurately reflects the rate in the Brazzaville population among women of reproductive age.

The transmission rate found in our study is among the highest reported in Africa, where rates range from 20 to 45% [8–13]. Very similar rates, 39%, were found in the first study from Kinshasa, Zaïre (1986–1987), and in a study from Lusaka, Zambia [9,10]. Comparisons, however, must be cautious. In Kinshasa, for example, children were defined as infected if they had a positive cord blood culture [9], while in Lusaka, they were classified as infected if they died with clinical AIDS or were seropositive at 2 years of age [10]. Our results are comparable with those of the Rwandan cohort studies, in which study design and criteria for HIV diagnosis were the same as in our study [8,12]. Rates in the Rwandan studies were substantially lower than those found in Brazzaville (24.7% in Kigali and 20.0% in Butare).

Cofactors of perinatal transmission may in part explain the differences in the rates observed across studies. For example, in the Zambian study and in the first Kinshasa study, where transmission rates were highest, a large proportion of women were symptomatic; in Zambia, 52% had AIDS-related complex (ARC) or generalized lymphadenopathy and in Kinshasa, 17% had AIDS [9,10]. In contrast, in a study performed later in Kinshasa (1989–1990), the proportion of symptomatic mothers was much lower, 1% with AIDS, 7% with ARC, as was the transmission rate (26%) [11].

Mortality in infants born to HIV-seropositive mothers was much higher than in similar cohort studies carried out in Europe and in North America [6,7,17–20]. These differences may be partly explained by the higher prevalence of nutritional deficiencies and the increased exposure of HIV-infected infants to infectious, parasitic and diarrheal diseases in developing countries [17]. This mortality rate is consistent with the findings of the first perinatal HIV study conducted in a population of similarly low socioeconomic status in Kinshasa, where infant mortality was 28% [9]. Mortality among infants born to HIV-1-positive mothers in our study contrasts sharply with mortality in the control group. Prematurity and low birth weight were more frequent in infants born to HIV-1-seropositive mothers than in control infants but most of these differences were attributable to the higher rate of twinning in the former group [21]. Moreover, infants in both groups received the same follow-up and close medical monitoring. Therefore, we believe that the excess of mortality in infants born to HIV-positive mothers, especially in singletons, was attributable to HIV infection. This is further supported by the similar transmission rates calculated with both the indirect and direct method, even when twins were excluded.

In our study, three infants, who were seronegative at 12 and 15 months, later seroconverted. Since no other risk factor for infection could be found, breast-feeding was the most probable route of infection. Although late transmissions were not included in the calculation of the transmission rate at 15 months, they may account for a significant number of infections in infants breastfed for a long time. Similar cases of secondary seroconversion have been described in Rwanda and Kenya [22,23].

We performed a sensitivity analysis to explore the effect on the rate of transmission with the assumption that the indeterminate infants were all infected or all uninfected. The resulting estimated rates were less than 10% above

or below the rates calculated by the direct and indirect methods. Nine indeterminate infants were lost to follow-up and 10 died before 15 months of conditions that did not meet the criteria of HIV-related death. No presumptions were made about their HIV status and it is most likely that the proportion of infected to uninfected infants was the same as among the infants with a definitive HIV status. Therefore, the median estimates with the indirect or direct methods are probably the most accurate.

The association between the presence of HIV-related symptoms in women and increased perinatal transmission, highly significant in our study, has not been so evident in other studies. However, other studies all show a similar trend. In our study, women were classified as symptomatic with any one sign of the WHO AIDS-case definition, while in other studies women were considered symptomatic if they had AIDS or ARC [9,10]. Assuming that the risk of transmission increases significantly in the very early symptomatic stages of HIV infection, a low threshold clinical criterion may best distinguish between low- and high-risk transmitters. Although the trend is still evident, a higher threshold criterion such as AIDS could diminish the strength of the association between symptoms and transmission.

Our finding that unmarried women or women whose relationship with their infant's father was brief were more at risk of transmitting the virus to their infants was similar to the observations made in a Rwandan study in which the risk of perinatal transmission increased significantly with the number of sexual partners prior to delivery [12]. Several hypotheses may account for this finding. Unmarried women and women in brief relationships may be more likely to be newly infected, with primary infection and seroconversion occurring at the beginning of their pregnancies. These women may also have been exposed to several viral strains. Infection with an additional strain of HIV might behave similarly to primary infection or to escape-mutant bursts of replication, resulting in either case in a higher risk of fetal transmission [24]. Finally, other sexually transmitted diseases (STD) may be more prevalent in these women although their role as a cofactor of perinatal transmission is still unclear. In the study from Butare, for example, the risk of transmission was significantly increased in women reporting a history of STD, but it was only weakly increased in women who were diagnosed with an STD during pregnancy [12].

To date, cohort studies have shown substantial variability in the rate of transmission reported in Africa. Among populations, the uneven distribution of maternal factors such as those revealed in our study probably accounts for some of the variability. Although the mechanisms and timing of perinatal transmission are unclear, several clinical trials aimed at interrupting perinatal transmission are already underway. Since the efficacy of any intervention strategy will probably differ depending on the precise nature of maternal cofactors and their relationship to the timing of transmission, they require further investigation.

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Appendix

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