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## ORIGINAL CONTRIBUTIONS

### Mother-to-Child Transmission of Human Immunodeficiency Virus Type 1 (HIV-1) and Its Determinants: A Cohort Study in Kigali, Rwanda

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The authors report the results of the first 2 years of follow-up of a prospective cohort study on the mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) and its determinants which started in November 1988 in Kigali, Rwanda. The study sample consists of 218 newborns of 215 HIV-1 seropositive women matched to 218 newborns of 216 HIV-1 seronegative women of the same age and parity. They were followed every 2 weeks during the first 2 years of follow-up. HIV-1 antibodies were detected by enzyme-linked immunosorbent assay and Western blot at 3-month intervals. Two methods of calculating the mother-to-child transmission rate were used: method 1 combines the information provided by the persistence of HIV-1 antibodies at 15 months of age in children born to HIV seropositive mothers and the excess mortality in this group compared with the cohort of children born to HIV seronegative mothers; method 2 is a case-by-case evaluation of all the children born to HIV seropositive mothers. A logistic regression model was used to study the determinants of transmission. The probability of survival at 24 months of age was 81% (95% confidence interval (CI) 75-86) in children born to seropositive mothers, compared with 95% (95% CI 92-98) in children born to seronegative mothers ( $p < 0.001$ ). The mother-to-child transmission rate calculated with method 1 was 25.7% (95% CI 18.8-32.5). With method 2, the medium estimate was 24.7%. In the multivariate analysis, a CD4/CD8 ratio  $< 0.5$  was the only maternal factor statistically associated with an increased risk of mother-to-child transmission of HIV-1 (odds ratio = 2.9, 95% CI 1.2-7.2). The authors' findings present evidence for a higher mother-to-child transmission rate of HIV-1 in children born in Rwanda than in industrialized countries. *Am J Epidemiol* 1993;137:589-99.

→ breast feeding; HIV infections; HIV-1; maternal-fetal exchange; risk factors

Infection with the human immunodeficiency virus type 1 (HIV-1) is now recog-

nized as a major public health problem in children, particularly in sub-Saharan Africa

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Abbreviations: CI, confidence interval; ELISA, enzyme-

linked immunosorbent assay; HIV-1, human immunodeficiency virus type 1; OR, odds ratio.

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(1). Most children acquire HIV infection from their mothers in utero, during delivery, or in the post-partum period through breast feeding (2-4). The rate of HIV-1 transmission from infected mothers to their offspring varies in published series from 13 percent to 45 percent, with a tendency toward higher rates in African studies (5-15). The reason for this variability between studies remains unclear. However, there is no commonly accepted method of calculation of the mother-to-child rate of HIV-1 transmission. Furthermore, until now few studies have addressed the issue of the determinants of perinatal transmission (5, 11, 16).

In November 1988, a prospective cohort study on the perinatal transmission of HIV-1 was undertaken in Kigali, the capital of Rwanda, Central Africa. In this city, the prevalence of HIV-1 infection among young adults of both sexes averages 30 percent (17). In this article, we report the key results of the first 2 years of follow-up of this cohort. Estimates of the rate of transmission of HIV-1 from infected mothers to their offspring have been made using methods recently pro-

posed by an International Working Group (18). Finally, we tried to shed light on the factors that might contribute to the observed level of transmission in this population.

## MATERIALS AND METHODS

### Study population

A prospective cohort study has been ongoing in Kigali, Rwanda, since November 1988. Details of the enrollment procedures have been published elsewhere (19). Briefly, HIV testing was offered between November 1988 and June 1989 to all women delivering in the Maternity Ward of the Centre Hospitalier de Kigali and fulfilling the following inclusion criteria: delivering a livebirth, living permanently within the city limits, and giving informed consent to participate. The study sample consists of 218 newborns of 215 HIV-1 seropositive women matched to 218 newborns of 216 HIV-1 seronegative women of the same age ( $\pm 2$  years) and parity ( $\pm 1$  pregnancy), who delivered during the same period.

The children and their mothers were followed every 2 weeks during the first 2 years of follow-up. They were either visited at home by a social worker or attended the outpatient clinic organized within the Mother and Child Health Clinic of the Centre Hospitalier de Kigali. A systematic clinical examination was performed by one of the pediatricians participating in the project every 3 months, and whenever necessary for medical care. All the children were immunized during the first 15 months of life following the recommendations of the Rwandese Expanded Programme of Immunization, with one exception: a high dose Edmonston-Zagreb measles vaccine was given at 6 months of age in the place of the Schwarz vaccine at 9 months (20, 21).

### Serologic methods

At delivery and at 3-month intervals thereafter, the child and mother's sera were tested for HIV-1 antibodies by a commercial enzyme-linked immunoadsorbent assay (ELISA) (EIA, Vironostika, Organon Tek-

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nika, Boxtel, the Netherlands). Samples that tested positive were further confirmed by a commercial Western blot technique (Du Pont, Wilmington, Delaware) using the Centers for Disease Control criteria of interpretation (22).

Mother's sera collected at delivery were tested for Chlamydiae antibodies by a commercial ELISA (Immuno Comb bi-spot, Produit Biotechnologie Strasbourg, Hillkirch, France) and for syphilis antibodies by non-treponemal test (VDRL, latex, Wellcome, Dartford, England) and treponemal test (TPHA, Wellcome). A recent syphilis infection was defined by dual positive VDRL and TPHA tests.

A blood sample was obtained from the mother 2 weeks after delivery. Mononuclear cell subpopulations were quantitated using an indirect immunofluorescence technique and monoclonal antibodies: OKT4 for helper-inducer T-cells (CD4) and OKT8 for suppressor-cytotoxic T-cells (CD8) (Ortho Diagnostic System, Raritan, New Jersey). A reversed CD4/CD8 ratio was considered as the criterion for impaired cellular immunity (23).

**Case definitions**

Criteria used to define children born to seropositive mothers as infected with HIV-1, uninfected, or with an indeterminate status are presented in table 1. The use of this classification was restricted to children who had or could have reached the cut-off age of 15 months at the time of analysis. It takes into account the HIV-1 antibody serostatus at 15 months of age and when the last contact occurred before 15 months of age, the presence or absence of signs and symptoms (18).

Death was defined as HIV-related either in a child with AIDS or in a child with at least one HIV-related sign/symptom when last seen and dying from severe infection or persistent diarrhea beyond the first 4 weeks of life. The following signs and symptoms were regarded as HIV-related: persistent diarrhea ( $\geq 14$  days), failure to thrive ( $< 80$  percent weight for age), persistent general-

**TABLE 1. Classification of children born to human immunodeficiency virus type 1 (HIV-1) seropositive mothers according to their probable HIV infection status, Kigali, Rwanda, 1988-1991**

HIV infection status	Definition
HIV-1 infected	HIV-1 antibody positive test* at age 15 months or HIV-related death† or acquired immunodeficiency syndrome (AIDS)†
HIV-1 non-infected	HIV-1 antibody negative test at age 15 months or HIV-1 antibody negative test at age $\geq 9$ months in child lost to follow-up without AIDS or HIV-1 antibody negative test at age $\geq 9$ months in a child who died from probable not HIV-related cause†
Indeterminate HIV-1 infection status	Death before 15 months with indeterminate relation to HIV infection† or child died of probable not HIV-related cause while seropositive or indeterminate before age 15 months or HIV-1 antibody negative test before age 9 months (when last seen) or child lost to follow-up while seropositive or indeterminate before age 15 months or seronegative before age 9 months (when last seen) or child with antibody indeterminate test and alive at age 15 months

\* Western blot result.

† See definition in Materials and Methods section.

ized lymphadenopathy, oral candidiasis (beyond the neonatal period), severe or recurrent pneumonia, chronic parotitis, and herpes zoster infection.

Children with at least two major and two minor signs of the World Health Organization (WHO) clinical case definition of pediatric acquired immunodeficiency syndrome (AIDS) (24) were considered to have AIDS. However, one modification was made to the WHO definition: if present, severe pulmonary infection (respiratory rate  $\geq 50$  in children 1–11 months old or  $\geq 40$  in children 12–23 months old) or recurrent pulmonary infection ( $\geq 2$  episodes during follow-up) was considered as a major sign in the place of chronic cough as a minor sign (25).

### Statistical methods

Probabilities of survival were computed according to the Kaplan-Meier product limit method. The 95 percent confidence intervals were calculated using Rothman's formula (26).

Two methods were used for calculating the mother-to-child transmission rate of HIV-1 (TR):

*Method 1.* A combination of the information provided by the persistence of HIV-1 antibodies at 15 months of age in children born to HIV-1 seropositive mothers and by the excess mortality in this group compared with the reference cohort constituted of children born to HIV-1 seronegative mothers (Method 1). Method 1 was originally proposed by Halsey et al. (14) in Haiti and was subsequently revised (18) to obtain the following equation:

$$TR = \frac{(m_1 - m_0) + [p * (1 - m_1)]}{(1 - m_0)},$$

where  $m_1$  = probability of dying before 15 months for children born to an HIV-1 seropositive mother;  $m_0$  = probability of dying before 15 months for children born to an HIV-1 seronegative mother; and  $p$  = proportion of surviving children born to HIV-1 seropositive mothers who are HIV-1 antibody positive at 15 months.

Standard deviations and 95 percent confidence intervals were computed for the es-

timate of TR obtained with this first method (18).

*Method 2.* A case-by-case evaluation of all the children born to HIV-1 seropositive mothers according to the classification presented in table 1 yields a direct estimate of TR with 95 percent confidence interval. To refine this method, three estimates of TR can be made when considering the three categories of children: infected ( $n+$ ), uninfected ( $n-$ ), and with indeterminate HIV-1 infection status ( $n?$ ). Let  $N$  denote the overall number of children born to HIV-1 seropositive mothers:

$$N = (n+) + (n-) + (n?).$$

A lower estimate of TR is:

$$TR_l = n+/N.$$

An medium estimate is:

$$TR_m = n+ / [(n+) + (n-)].$$

An upper estimate is:

$$TR_u = [(n+) + (n?)]/N.$$

After univariate analysis, a logistic regression model was used to assess the association between pediatric HIV-1 infection (defined as above in method 2) and explanatory covariates grouped in four categories: history of adverse pregnancy outcome (defined by the proportion of stillbirths and abortions out of the total number of pregnancies), maternal clinical and immunologic status, circumstances of delivery of the mothers and sexually transmitted diseases diagnosed at the time of delivery. The factors found to have a  $p$  value  $< 0.30$  in the univariate analysis were included in the model. This analysis was performed with the EGRET software (Statistical Epidemiology Research Corporation, Seattle, Washington).

## RESULTS

### Survival experience of the cohort and analysis of the causes of death

Out of 218 newborns of HIV-1 seropositive mothers, 40 (18.3 percent) died and 21

(9.6 percent) were lost to follow-up during the first 24 months of life. Altogether, this cohort of children accounts for 4,392 months of follow-up, i.e., 366 child-years. Among the 21 children lost to follow-up, only nine (4.1 percent) were lost before they could be classified as HIV-1 infected or uninfected (table 2).

Out of 218 newborns of HIV-1 seronegative mothers, 10 (4.6 percent) died (including one who seroconverted postnatally to HIV-1 (4)) and 15 (6.9 percent) were lost to follow-up during the first 24 months of life.

Altogether, this cohort of children born to HIV-1 seronegative mothers accounts for 4,924 months of follow-up, i.e., 410 child-years (table 2).

All the children were breast-fed from birth. The proportion of children who were still breast-fed remained high at 12 and 24 months, 88 percent and 68 percent respectively, without any difference between the two cohorts.

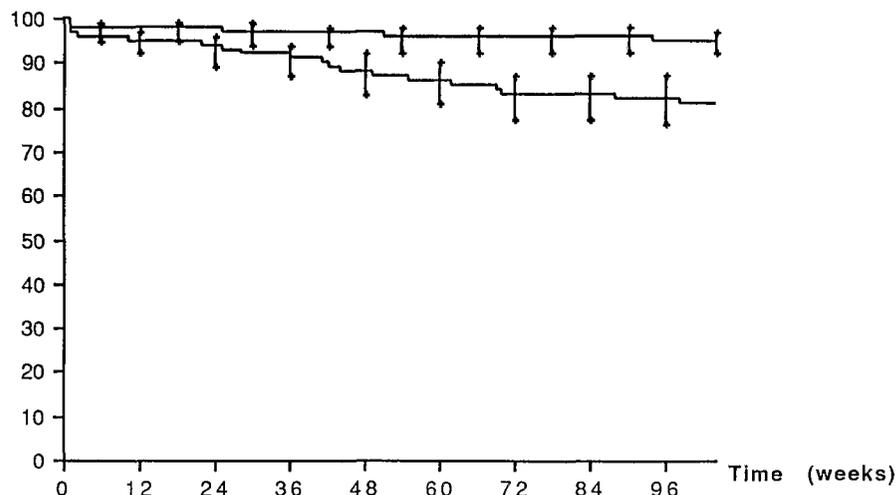
Figure 1 shows the cumulative probability of survival of children born to HIV-1 seropositive and HIV-1 seronegative mothers

**TABLE 2. Summary of the first 2 years of follow-up of the cohort of children born to human immunodeficiency virus type 1 (HIV-1) positive and negative mothers, Kigali, Rwanda, 1988-1991**

Time after birth	Children born to					
	HIV-1 positive mothers			HIV-1 negative mothers		
	No. of deaths	Loss to follow-up	Child-months	No. of deaths	Loss to follow-up	Child-months
0-90 days*	11	0	629	4	0	642
4-6 months	4	4	610	2	1	639
7-9 months	4	5	583	1	1	629
10-12 months	8	3	547	2	2	625
13-15 months	4	1	528	0	4	610
16-18 months	5	0	512	0	1	601
19-21 months	1	5	500	0	5	595
22-24 months	3	3	483	1	1	583
Total	40	21	4,392	10	15	4,924

\* 1-3 months.

**Probability of survival (%)**



**FIGURE 1.** Cumulative probability of survival 24 months after birth in children born to human immunodeficiency virus type 1 (HIV-1) seropositive and seronegative mothers, Kigali, Rwanda, 1988-1991. The upper curve shows the probability of survival of children born to HIV-1 seronegative mothers. The lower curve shows the probability of survival of children born to HIV-1 seropositive mothers.

during the first 2 years of follow-up. A statistically significant difference in survival rate was found between the two groups, with a probability of survival of 81 percent (95 percent CI 75–86) at 24 months of age in children born to HIV-1 seropositive mothers, in contrast to a probability of survival of 95 percent (95 percent CI 92–98) in children born to HIV-1 seronegative mothers ( $p < 0.001$ , log-rank test).

Table 3 summarizes the causes of deaths among children born to HIV-1 seropositive and HIV-1 seronegative mothers, during the first 24 months of follow-up. In children born to HIV-1 seropositive mothers, diarrheal diseases and pulmonary infections accounted for 53 percent of the deaths occurring in the first 2 years of life (table 3). Four of the 10 deaths among children born to HIV-1 seronegative mothers occurred in the early neonatal period (first week of life). Among the 40 children born to HIV-1 seropositive mothers who died, 23 (57.5 percent) were classified as HIV-1-infected, 16 (40 percent) had an indeterminate status for HIV-1 infection and one (2.5 percent) was considered as uninfected. This latter child died of fever of unknown origin.

### Loss of maternal HIV-1 antibodies

Figure 2 shows the follow-up data on the rate of loss of maternal HIV-1 antibodies according to the age of the children. At birth, 100 percent of children had antibodies to HIV-1. At 12 months of age, 20 percent of the surviving children had HIV-1 antibodies, while at 15 months of age, 17 percent had HIV-1 antibodies. No loss of HIV-1 antibodies occurred after 15 months of age. The mean duration of HIV-1 antibody persistence was 250 days (8.2 months) (median, 226 days; range, 66–490 days).

### Mother-to child transmission rate of HIV-1

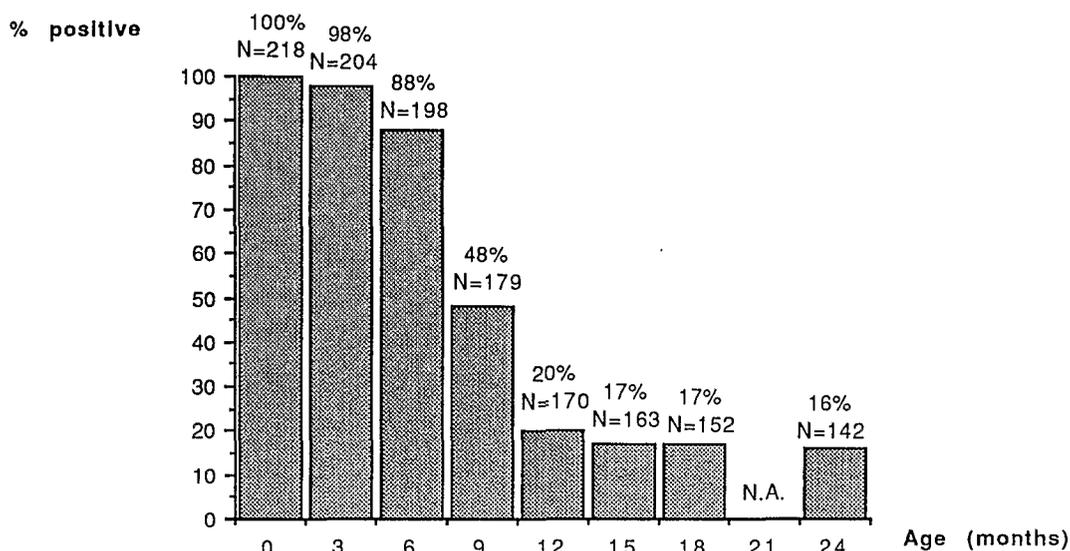
The cumulative probability of death at 15 months of age was 14.6 percent in the cohort of children born to HIV-1 seropositive mothers and 4.1 percent in the cohort of children born to HIV-1 seronegative mothers, giving a 10.5 percent excess mortality in the HIV-1-exposed group. When this excess mortality figure is combined to the 17 percent Western blot positivity observed at 15 months of age (figure 2), the estimated rate of mother-to-child transmission, calculated

**TABLE 3. Causes of death among the children of the cohort of mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1), Kigali, Rwanda, 1988–1991**

	Children born to HIV-1 seropositive mothers			Children born to HIV-1 seronegative mothers
	Indeterminate HIV infection status	HIV-uninfected	HIV-infected*	
Diarrhea:				
Acute	4		1	
Persistent*			7	1
Total	4		8	1
Pneumonia	3		6	2
Congenital malformation	4			
Fever of unknown origin		1	3	
Prematurity/dysmaturity	3			2
Sepsis/meningitis			2	2
Severe malaria			2	1†
Other cause	1		1	1
Unknown	1		1	1
Total	16	1	23	10

\* See definition in Materials and Methods section and table 1.

† Postnatal mother-to-child seroconversion (see reference 4).



**FIGURE 2.** Loss of maternal human immunodeficiency virus antibodies according to age in children born to HIV-1 seropositive mothers, Kigali, Rwanda, 1988–1991. Percent positive by Western blot antibody test. NA, no specimen available.

with method 1, was 25.7 percent (95 percent CI 18.8–32.5).

With method 2, 46 (21.1 percent) of the 218 children born to HIV-1 seropositive mothers, were classified as HIV-1-infected and 140 (64.2 percent) as uninfected. For 32 children (14.7 percent), the HIV-1 infection status remained indeterminate. This subgroup is made of 14 children who died before 15 months with indeterminate relation to HIV-1 infection, two children who died of probable not HIV-1-related cause while seropositive before 15 months, nine children who were lost to follow-up while seropositive before 15 months, and seven children who were known to be alive at 24 months of age but could neither be examined clinically nor tested for the presence of HIV-1 antibodies. Thus, three estimates of TR can be made with their 95 percent CI:  $TR_i = 21.1$  percent (15.7–26.5);  $TR_m = 24.7$  percent (18.5–30.9);  $TR_u = 35.8$  percent (29.4–42.1).

#### Determinants of mother-to-child transmission of HIV-1

Among the 218 children born to HIV-1-positive mothers, the HIV-1 infection status

was ascertained for 186 of them (46 infected and 140 uninfected). All the items selected for the multivariate analysis were completed for 135 children (30 children infected and 105 children uninfected). There was no significant difference on the inclusion and follow-up characteristics between these 135 children and the 51 others.

In the univariate analysis, the clinical status of the mother at delivery and during the 15 first months of follow-up (asymptomatic, symptomatic with regard to HIV-1 infection, or clinical AIDS) and the mode of delivery were not related to HIV-1 infection in the child ( $p$  value = 0.94 and 0.64, respectively).

We included in the logistic regression model the following variables: recent syphilis ( $p = 0.10$  in univariate analysis), Chlamydiae infection ( $p = 0.30$ ), advanced maternal age greater than 25 years ( $p = 0.24$ ), adverse pregnancy outcome ( $p = 0.035$ ), and CD4/CD8 ratio  $<0.5$  ( $p = 0.01$ ).

In the multivariate analysis, only a CD4/CD8 ratio  $<0.5$  remained statistically associated with an increased risk of mother-to-child transmission of HIV-1 (table 4). Thus, HIV-1 seropositive mothers with severe immunosuppression were 2.9 times more likely

**TABLE 4. Maternal variables studied as possible determinants of mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) in 135 children born to seropositive mothers, Kigali, Rwanda, 1988-1991**

Variable	Frequency (%) in HIV-1- infected* children (n = 30)	Frequency (%) in uninfected* children (n = 105)	Odds ratio†	95% confidence interval	p value†
CD4/CD8 ratio <0.5	13 (43)	21 (20)	2.88	1.15-7.22	0.024
History of at least one abortion or stillbirth	12 (40)	22 (21)	2.12	0.85-5.28	0.108
Age >25 years	15 (50)	40 (38)	1.80	0.74-4.35	0.195
Recent* syphilis in- fection	4 (13)	5 (5)	2.55	0.56-11.6	0.225
<i>Chlamydiae</i> infection	7 (23)	16 (15)	1.18	0.39-3.57	0.775

\* See definition in Materials and Methods section.

† Computed by logistic regression model.

to transmit HIV-1 infection to their offspring than HIV-1-infected women without severe immunologic impairment. Although a trend existed for the others factors tested, none of them reached the level of statistical significance.

## DISCUSSION

This cohort study shows that in Rwanda, mortality among children born to seropositive mothers is high in the first 2 years of life, occurs early, and is principally due to diarrheal diseases and pulmonary infections. This mortality rate (19 percent for the first 2 years of life), although lower than in other African studies (5, 7) is two- to threefold higher than among European children born to HIV-1 seropositive mothers (10, 11). Diarrheal diseases and pulmonary infections, the principal causes of death in children under age 5 years in the developing world (27, 28), are also the major causes of death in children born to seropositive mothers in this study. Therefore, the increased mortality in children born to seropositive mothers in Africa may, at least in part, be explained by greater exposure to enteric and respiratory pathogens. As seropositive and seronegative mothers in our sample were similar in terms of socioeconomic status and parity (19), we assume that the high rate of mortality in children born to HIV-1 seropositive mothers is related with maternal HIV-1 infection. Among the children born

to seronegative mothers, the mortality during the first 2 years is lower than expected in Rwandan children. This finding is probably related to the regular follow-up and improved medical care provided to the children in our cohort. This is consistent with mortality experience documented in the other African studies (5, 7) of mother-to-child transmission of HIV-1.

In this study, HIV-1 infected and uninfected children were immunized with a high-dose Edmonston-Zagreb measles vaccine at 6 months of age (20). A recent study from Senegal strongly suggests that child mortality is higher among those receiving high-dose measles vaccines than among those given the standard vaccine (29). A follow-up of the survival experience of the cohort is therefore planned until 48 months of age to confirm the low mortality figures presented in this report for the first 2 years of follow-up.

Half of the children born to HIV-1 seropositive women in our cohort have lost their maternally acquired antibodies at 9 months of age. This is consistent with other studies either in Africa (5) or in the United States (13). We can consider that in our sample, the loss of maternal antibodies is virtually achieved at 12 months of age.

In this prospective cohort study, the transmission rate of HIV-1 from mother to child was 25.7 percent with method 1 and 24.7 percent with method 2 (medium estimate) with 95 percent confidence intervals yielding

a range of possible values of 18 percent to 31 percent. These figures are in the low range of other perinatal studies carried out in Africa (Kinshasa, Zaire, 39 percent (5); Lusaka, Zambia, 39 percent (6); Brazzaville, Congo, 52 percent (7)). By contrast, most perinatal studies from industrialized countries have documented lower transmission rates. The largest published study, the European Collaborative Study, has analyzed a cohort of 372 children of seropositive mothers born at least 18 months before the analysis from 10 different centers in Europe; the mother-to-child transmission rate was 14.4 percent in this group of children (16). In the French Collaborative Study, the transmission rate of 528 children with sufficient follow-up is currently estimated at 19 percent (18). It should, however, be emphasized that comparisons between studies are made difficult because the methods of calculating the mother-to-child transmission rates are different from one study to another (18). We used two different methods to estimate the rate of transmission. The case-by-case evaluation (method 2) should be considered as a reference method, is applicable in any setting, and can be used for the study of the determinants of transmission. However, this method yields a number of children with indeterminate status for HIV-1 infection. In our study, 15 percent of the children born to HIV-1 seropositive mothers remained with an indeterminate HIV-1 infection status. Although this can be considered as acceptable, the consequence is a wide range of values of the transmission rate with lower, medium and upper estimates. The other method (method 1) is an attempt to solve the problem of the case-by-case classification. It requires a comparison group. The use of method 1 has been challenged on the grounds that uninfected infants born to seropositive mothers might be at higher risk of mortality independently of HIV-1 infection and that, consequently, the method would overestimate the transmission rate (3). It is worth noting that, in our study, the two methods gave comparable estimates of the rate of transmission. With both methods, we report estimates of the transmission rate

with possible ranges of values and confidence intervals. We believe that this approach should be preferred and that other investigators may experience the same variability around their point estimate if such computations were done.

It has been suggested that bias toward a higher rate of transmission was introduced in some African studies with a high rate of loss to follow-up (3). However, in the present study, the loss to follow-up rate did not exceed 4 percent when we consider the period during which children lost to follow-up remain with an indeterminate status for HIV-1 infection. If one admits that bias was limited in this cohort study, one could discuss the reasons for the discrepancy in rates of transmission between this study and other African studies on one hand, and the European Collaborative and French studies on the other hand.

It is plausible that African HIV-1-infected mothers have on the average worse health status than seropositive mothers from industrialized countries and might therefore transmit HIV-1 more efficiently to their offspring. However, in all but one study (5) among the perinatal studies from Africa, the vast majority of women were asymptomatic at the time of enrollment (6-8). Although none of the seropositive mothers in our study had AIDS at enrollment (19), the majority had evidence of cell-mediated immunologic impairment. Indeed, 72 percent of the seropositive mothers had a CD4/CD8 ratio lower than 1 when tested 15 days after delivery; a third of those had a CD4/CD8 ratio lower than 0.5 (19). It is therefore conceivable that immunologic deficiency is more prevalent among HIV-1 infected women in Africa due to their nutritional status or the infectious environment.

The longer time interval since contamination in populations where HIV-1 has been circulating for several years is another possible explanation for the high frequency of low CD4/CD8 ratios encountered in our sample. The role of a reversed maternal CD4/CD8 ratio or a decreased CD4 cell count as risk factors of mother-to-child transmission has recently been demon-

strated in the European Collaborative Study (16). In our study, mothers with a CD4/CD8 ratio lower than 0.5 transmitted HIV-1 infection more frequently to their infants, as shown in both univariate and multivariate analyses.

Other maternal factors, such as clinical status, mode of delivery, or sexually transmitted diseases were not associated with increased risk of transmission. It is possible that as few women in our sample were symptomatic at delivery, a difference was impossible to document for this factor. The same limitation has been encountered for mode of delivery, with few cesarean sections performed in the study sample. A history of adverse pregnancy outcome was related with pediatric HIV-1 infection in the univariate analysis but not in the multivariate analysis. This variable could be an indicator of length of maternal HIV-1 infection and not a determinant of transmission. Finally, no other maternal factor than the CD4/CD8 ratio remained important in the multivariate model, reflecting their limited contribution to mother-to-child transmission of HIV-1 in contrast to the European Collaborative Study findings (16). We decided not to include in the analysis low birth weight and prematurity as possible determinants of transmission. Indeed, the causal pathway between these events and pediatric HIV-1 infection is speculative.

The role of breast feeding in mother-to-child postnatal HIV-1 transmission is now well established (4, 16, 30-37). Breast feeding was universal and prolonged in our population as well as in the other African studies (5-7), whereas only 5 percent of European women enrolled in such studies breast-fed, usually for a short period (11, 16). In our study, HIV-1 infected cells were detected by the polymerase chain reaction test in 47 percent of breast milk samples of seropositive mothers tested 15 days after delivery (38). Quantitating the excess risk attributable to breast feeding among children whose mothers are seropositive for HIV-1 at the time of delivery is extremely difficult for numerous methodological and ethical reasons (39) and cannot be done in the present study.

In conclusion, our findings are consistent with other studies from Africa and present evidence for a higher mother-to-child transmission rate of HIV-1 in children born in Africa than in industrialized countries. This difference in rate might result from different clinical/immunologic characteristics of the mothers and/or from postnatal transmission of HIV-1 through breast milk. Studies are needed to better define the clinical and immunologic characteristics of mothers enrolled in perinatal studies and to evaluate the additional risk of breast feeding among infants of seropositive women.

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