

# Natural History of Human Immunodeficiency Virus Type 1 Infection in Children: A Five-Year Prospective Study in Rwanda

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**ABSTRACT.** *Objective.* To compare morbidity and mortality of human immunodeficiency virus type 1 (HIV-1)-infected and HIV-1-uninfected children and to identify predictors of acquired immunodeficiency syndrome (AIDS) and death among HIV-1-infected children in the context of a developing country.

*Design.* Prospective cohort study.

*Setting.* Maternal and child health clinic of the Centre Hospitalier de Kigali, Rwanda.

*Participants.* Two hundred eighteen children born to HIV-1-seropositive mothers and 218 born to seronegative mothers of the same age and parity were enrolled at birth.

*Outcome Measures.* Deaths, clinical AIDS, nonspecific HIV-related manifestations, and use of health care services.

*Results.* Fifty-four infected and 347 uninfected children were followed up for a median of 27 and 51 months, respectively. With the exception of chronic cough, the risk of occurrence of nonspecific HIV-related conditions was 3 to 13 times higher in infected than in uninfected children. The recurrence rate and severity of these findings were increased systematically in infected infants. Estimated cumulative risk of developing AIDS was 28% and 35% at 2 and 5 years of age, respectively. Estimated risk of death among infected children at 2 and 5 years of age was 45% and 62%, respectively, a rate 21 times higher than in uninfected children. Median survival time after estimated infection was 12.4 months. Early infection, early onset of HIV-related conditions, failure to thrive, and generalized lymphadenopathy were associated with subsequent risk of death and/or AIDS, whereas lymphoid interstitial pneumonitis was predictive of a milder disease.

*Conclusions.* In Africa, HIV-1-infected children develop disease manifestations early in life. Specific clinical findings are predictive of HIV-1 disease, AIDS stage, and death. Bimodal expression of HIV-1 pediatric disease is encountered in Africa, as in industrialized countries, but prognosis is poorer. *Pediatrics* 1999;104(5). URL: <http://www.pediatrics.org/cgi/content/full/104/5/e56>; *human immunodeficiency virus infection, children, vertical transmission, natural history, Africa.*

ABBREVIATIONS. WHO, World Health Organization; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; AIDS, acquired immunodeficiency syndrome; PCR, polymerase chain reaction; HR, hazard ratio; CI, confidence interval.

According to the World Health Organization (WHO), 1.1 million of children were living with human immunodeficiency virus (HIV) infection worldwide at the end of 1997.<sup>1</sup> Of these, the great majority live in sub-Saharan Africa and were infected by their mother during pregnancy, delivery, or breastfeeding. Data on the natural history of human immunodeficiency virus type 1 (HIV-1) infection in children followed prospectively from birth and prognostic studies are scarce in developing countries. Available reports show a high variability in mortality and morbidity indicators according to the study settings and a probable bimodal evolution of pediatric HIV disease.<sup>2-5</sup> A better understanding of the clinical course and of the predictors of disease progression is needed to improve diagnosis and treatment of HIV-1 perinatally infected children in developing countries, an area vastly unexplored.<sup>5</sup>

A prospective cohort study on the perinatal transmission of HIV and the natural history of HIV-1 infection was conducted in Kigali, the capital of Rwanda, from 1988 to 1994.<sup>6,7</sup> This report describes the clinical and immunologic findings in the first 5 years of life of the 436 children enrolled in this cohort.

## METHODS

### Study Site, Population, and Follow-up

Details about enrollment and follow-up procedures in the cohort have been described elsewhere.<sup>6</sup> Briefly, 218 infants born to 215 HIV-seropositive mothers were enrolled at birth between November 1988 and June 1989 at the maternity ward of the Centre Hospitalier de Kigali. A comparison group of 218 children born to HIV-seronegative mothers of the same age and parity were enrolled simultaneously.

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The children and their mothers were followed every 2 weeks during the first 2 years of life and every 4 weeks thereafter. Thus, during 5 years, they were visited regularly at home by a social worker or they attended the outpatient clinic organized within the Mother and Child Health Clinic of the Centre Hospitalier de Kigali. In addition, the children were systematically examined by a pediatrician every 3 months and assessed for HIV-related signs and symptoms. The following conditions were regarded as HIV-related: chronic diarrhea ( $\geq 14$  days); chronic cough ( $\geq 14$  days); chronic fever ( $\geq 14$  days); severe or recurrent pneumonia; hepatomegaly; splenomegaly; generalized dermatitis; lymphoid interstitial pneumonitis; oral candidiasis (beyond the neonatal period); chronic parotitis; persistent generalized lymphadenopathy (lymph nodes measuring  $\geq 0.5$  cm and present in two or more extra inguinal sites); and failure to thrive ( $< 80\%$  of weight for age). When necessary, children were seen in the outpatient department or hospitalized in the pediatrics department and treated free of charge. All of the children were immunized during the first 15 months of life, following the recommendations of the WHO Expanded Program of Immunization with one exception: a high dose Edmonston-Zagreb measles vaccine was given at 6 months of age in place of the Schwarz vaccine given at 9 months of age.<sup>8</sup> The physicians and social workers were blinded to the HIV infection status of the children up to 18 months of age.

### Laboratory 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 immunosorbent assay, further confirmed by a commercial Western Blot technique if the test was positive. As maternal seroconversion may have occurred during follow-up, children born to HIV-negative mothers may have become exposed to vertically acquired infection through breastfeeding and become subsequently infected. Polymerase chain reaction (PCR) testing for diagnosis of HIV-1 infection was performed on all available samples, collected routinely from birth using a home-made combination of primers of the gag and pol regions of the genome. Detailed description and information on performances of this PCR technique, which reached sensitivity and specificity levels of 100% and 98%, respectively, have been described elsewhere.<sup>9,10</sup> Blood for total lymphocyte and CD4/CD8 count by a manual indirect immunofluorescent method was obtained 15 days after delivery in mothers and at 6 months of age in children.

### Definition of Pediatric HIV Infection and Classification of the Children

Children were considered HIV-1-infected (group 1) if they had at least one positive PCR result during follow-up, regardless of clinical and serologic criteria. Children who had a positive PCR test at birth were considered infected from their first day of life, whereas for other children, the infection date was estimated as the median date of the interval between the last negative and the first positive PCR test result. All infected children had a seropositive mother, diagnosed either at delivery or after seroconversion during follow-up.

Children were considered HIV-uninfected if they had no positive PCR test result and either 1) they were negative for HIV antibody at 15 months of age and did not fulfill the modified WHO clinical case definition of pediatric acquired immunodeficiency syndrome (AIDS), in which severe and/or recurrent pulmonary infection is considered a major sign in place of chronic cough as a minor sign<sup>11,12</sup> during the follow-up, or 2) they died before 15 months of age, they were HIV-seronegative, and their death was not considered HIV-related (death was defined as HIV-related either in a child fulfilling the modified WHO clinical definition of pediatric AIDS or in a child with at least one HIV-related condition when last seen and dying from severe infection or persistent diarrhea beyond the first 4 weeks of life). Uninfected children were either born to seropositive (group 2) or seronegative mothers (group 3). The HIV infection status of children was considered indeterminate (group 4) otherwise.

### Statistical Analysis

HIV infection was treated as a time-dependent variable so that infected children, estimated to have been contaminated after birth, were considered uninfected until the last quarterly examination

preceding their infection and were considered infected thereafter. Morbidity and mortality outcomes were described using the Kaplan-Meier method. The two groups of uninfected children (groups 2 and 3) were first compared. When appropriate, all uninfected children were compared with the infected ones (group 1). Mortality, nonspecific HIV-related morbidity, and use of health care services (outpatient clinic, hospital ward, and medical injections) were compared by univariate analyses, using the Log-rank test, and by multivariate analyses, using the Cox proportional hazards model with HIV infection considered to be time varying. Entry time was the date of birth for all children. Multivariate analyses were performed using descending stepwise procedures after inclusion of all variables associated to the variable of interest in univariate analysis with a significance level  $< 20\%$ . We defined the recurrence rate of each type of HIV-related condition and medical service provided as the proportion of 3-month periods or quarters with the event present in each group, normalized to rates per 100 child-quarters. Risk ratios then were computed by dividing recurrence rates of the different groups compared. A prognostic analysis restricted to HIV-infected children was performed by Cox proportional hazard models to identify predictive factors of death and of the development of AIDS.

## RESULTS

Of the 436 eligible children, 54 were diagnosed as infected (group 1); 45 of these children were born to HIV-infected mothers, and the remaining 9 children were born to women who were uninfected at delivery but who became HIV-seropositive during the follow-up, and thus became themselves infected too.<sup>12</sup> A total of 347 children were considered uninfected: 138 were born to HIV-infected women (group 2) and 209 to HIV-uninfected women (group 3). The remaining 35 children, born to seropositive mothers, had an indeterminate infection status and were excluded from the following analysis.

Among the 54 infected children, 39 were estimated to have been contaminated in utero, intrapartum, or during their first 3 months of life and thus were considered as infected throughout their follow-up. The remaining 15 children, who were thought to have been contaminated later in life, were considered infected only from the 3-month period of their estimated contamination: second (2), fourth (9), fifth (2), sixth (1), and seventh quarters (1), respectively. The median estimated age at infection among the 54 infected children was 1.6 months.

Overall, the median follow-up time was 27.4 months in group 1 (range: 4.5–58.2 months), 51.5 months in group 2 (range: 8.9–58.1 months), and 51.4 months in group 3 (range: 0.03–58.6 months). At the end of the study period, 6 children had been lost to follow-up from group 1 (11.1%), 17 from group 2 (12.3%), and 25 from group 3 (12.0%).

Male to female sex ratio was 1 overall, without difference among the three groups combined. All but 4 children were breastfed for a median duration of 18 months (range: 1.2–38.9 months). None of the infected children received antiretroviral therapy or opportunistic infection prophylaxis.

Among the 215 HIV-infected women, only 1 presented clinical AIDS at inclusion. The median CD4 cell count at 2 weeks after delivery was  $757/\text{mm}^3$  (range: 179–2992).

### Comparison of the Two Groups of Uninfected Children

Comparisons between uninfected children born to seropositive women (group 2) and uninfected chil-

dren born to seronegative women (group 3) showed that these two groups did not differ with respect to mortality during the 5 years of follow-up (Cox hazard ratio [HR] of death for children of group 2 compared with children of group 3: 0.4, 95% confidence interval [CI]: 0.1–1.6;  $P = .20$ ). Comparison of morbidity between these two groups showed that the risk of onset during follow-up of most of the HIV-related conditions studied was strictly comparable between children of group 2 and children of group 3 (data not shown). The risk of occurrence of three clinical manifestations tended to increase among uninfected children born to seropositive mothers, compared with unexposed children: severe pneumonia (HR for children of group 2, compared with children of group 3: 1.4; 95% CI: 0.9–2.0;  $P = .12$ ), generalized dermatitis (HR: 1.7; 95% CI: 0.9–2.5;  $P = .11$ ), and chronic parotitis (HR: 3.3; 95% CI: 0.7–9.9;  $P = .12$ ). Children of group 2 also tended to have an increased risk of hospitalization during follow-up (HR: 1.3; 95% CI: 0.9–1.4;  $P = .10$ ). Considering that these differences were not statistically significant, the remainder of the analysis considered uninfected children of groups 2 and 3 as a whole and consisted in their comparison to infected children of group 1.

### Mortality

Twenty-eight (52%) infected children and 13 (4%) uninfected children died during follow-up. Figure 1 shows the Kaplan-Meier estimate of survival curves of the children, according to their infection status. The probability of death in infected children was 0.26 (95% CI: 0.16–0.41) at first birthday, 0.45 (95% CI: 0.32–0.60) at 2 years of age, and 0.62 (95% CI: 0.47–0.78) at 5 years of age. The estimated cumulative probability of death in uninfected children was 0.04 (95% CI: 0.02–0.07) at 5 years of age. The univariate Cox proportional hazards model estimated that the overall risk of death was 20.7 times higher in infected children than in uninfected children (95% CI: 10.7–40.0). Median age at death was 13.4 months for infected ( $n = 28$ ) and 7.7 months for uninfected children ( $n = 13$ ). The median time of survival was 12.4 months after estimated infection and 6.1 months after occurrence of the first HIV-related condition in the 28 infected children who died. Risk of death among children infected in the first 3 months of life was 5.1 times higher than among those who acquired infection later (95% CI: 1.5–17.0). The most common

causes of death among infected children were pulmonary infections (9 cases) and diarrhea (8 cases).

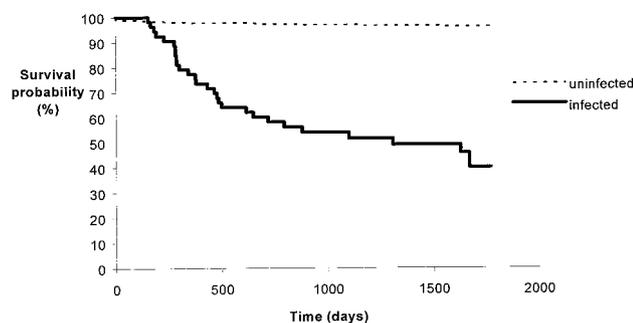
### AIDS Diagnosis

Of the 54 HIV-infected children, 14 (26%) developed AIDS, according to the modified WHO clinical definition. The cumulated probabilities of the development of AIDS at 1, 2, and 5 years of age were 0.17 (95% CI: 0.09–0.32), 0.28 (95% CI: 0.17–0.45), and 0.35 (95% CI: 0.22–0.53), respectively. The median duration of HIV infection without AIDS was 13.9 months from the estimated date of contamination. Among the 28 infected children who died, 9 met the case definition of AIDS. The median time of survival after the occurrence of AIDS was 9 months (range: 4–21 months).

### HIV-related Signs and Symptoms

All 54 infected children presented at least one non-specific HIV-related condition during follow-up. From the estimated date of contamination, median time of infection without any HIV-related condition was 5.3 months (range: 0–13.3 months). Estimated age at onset of the first HIV-related condition was 8.9 months. The initial clinical signs that occurred most frequently were failure to thrive (51.9%) and persistent lymphadenopathy (44.4%). These conditions occurred either alone or in combination with other clinical manifestations: 34 children (63%) first presented with one sign or symptom, 11 (20%) with two, and 9 (17%) with three to six conditions. Morbidity was not different between the 39 children infected perinatally and the 15 children infected after 3 months of age (data not shown).

The occurrence of nonspecific HIV-related signs and symptoms in the first 5 years of life is described for infected and uninfected children in Table 1. Study time was first divided into two periods (before and after 2 years of life), and comparisons between these two periods within each group of children showed that risks of onset of the different manifestations were approximately constant over time (data not shown). The most frequent signs among infected children were chronic cough, persistent generalized lymphadenopathy, and failure to thrive, which were estimated to occur at least once in 97%, 93%, and 92% of the infected children, respectively. All of the HIV symptomatic conditions studied also occurred among uninfected children, although the risk of onset among uninfected children was significantly lower (3–13 times) than among infected children, except for chronic cough, which occurred in almost all of the children, regardless of their HIV infection status. The clinical features for which recurrence had the greatest ability to discriminate infected from uninfected children were oral candidiasis and chronic parotitis: they were found almost 20 times more frequently in infected than in uninfected children. All of the other conditions, including chronic cough, occurred significantly more often in infected than in uninfected children but were less specific of HIV infection. When present, chronic parotitis, generalized dermatitis, splenomegaly, and persistent



**Fig 1.** Time to death, according to Kaplan-Meier estimate in 54 HIV-infected and 347 uninfected children. The Mother-to-Child HIV-1 Transmission Study cohort, Kigali, Rwanda, 1988–1994.

**TABLE 1.** Five-Year Cumulative Frequency, Risk of Onset, Median Age at First Onset, and Recurrence Rate of Nonspecific HIV-related Conditions in 54 HIV-infected Children in Comparison With 347 Uninfected Children. The Mother-to-Child HIV-1 Transmission Study Cohort, Kigali, Rwanda, 1988–1994

Diagnosis	Number		Risk of Onset* (95% CI)		HR (Cox Model) (95% CI)	Median Age at Onset (Months)		Recurrence Rate/100 Child-Quarters		RR† (95% CI)
	Infected	Uninfected	Infected	Uninfected		Infected	Uninfected	Infected	Uninfected	
	Oral candidiasis	19	16	0.5 (0.4–0.7)	0.05 (0.03–0.1)	12.7 (6.5–24.8)	11.8	9.0	6.3	0.3
Chronic parotitis	7	8	0.4 (0.2–0.8)	0.03 (0.01–0.1)	11.1 (4.0–30.8)	24.0	47.9	2.8	0.2	18.1 (7.1–49.8)
Hepatomegaly	28	59	0.8 (0.6–0.9)	0.2 (0.1–0.2)	6.6 (4.1–10.4)	11.9	15.0	12.4	1.3	9.5 (6.6–13.5)
Generalised dermatitis	25	53	0.7 (0.5–0.8)	0.2 (0.2–0.3)	6.5 (4.0–10.6)	12.4	18.1	12.0	1.4	8.5 (6.0–12.1)
Chronic fever	11	22	0.4 (0.2–0.6)	0.1 (0.1–0.2)	5.9 (2.8–12.1)	20.8	23.5	2.8	0.5	5.8 (2.8–11.6)
Chronic diarrhea	23	53	0.7 (0.5–0.9)	0.2 (0.2–0.3)	5.4 (3.3–8.8)	18.0	19.5	7.9	1.8	4.5 (3.0–6.5)
Lymphoid interstitial pneumonitis	20	54	0.7 (0.5–0.8)	0.2 (0.1–0.2)	4.9 (2.9–8.1)	20.9	20.9	6.1	1.2	5.2 (3.2–8.1)
Splenomegaly	21	54	0.6 (0.4–0.7)	0.2 (0.1–0.2)	4.3 (2.6–7.2)	6.1	14.9	6.1	1.4	4.4 (2.8–6.8)
Lymphadenopathy	39	200	0.9 (0.8–1.0)	0.7 (0.7–0.8)	3.5 (2.5–5.0)	9.7	20.7	33.2	7.3	4.6 (3.8–5.5)
Severe pneumonia	22	87	0.7 (0.5–0.8)	0.3 (0.2–0.3)	3.0 (1.9–4.8)	14.9	17.7	11.6	3.3	3.5 (2.6–4.8)
Failure to thrive	45	193	0.9 (0.8–1.0)	0.6 (0.5–0.7)	2.8 (2.0–3.9)	9.5	11.9	43.7	17.9	2.4 (2.1–2.8)
Chronic cough	45	332	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.9 (0.7–1.2)	9.0	6.2	28.1	22.0	1.3 (1.1–1.5)

\* Kaplan-Meier estimate of the cumulated risk of onset of at least one episode of a given condition during the 5 years of follow-up.

† Ratio of recurrence rates (infected/noninfected).

lymphadenopathy tended to occur earlier in infected than in uninfected children.

### Contacts With the Health Care System

Table 2 shows the estimated proportions of infected and uninfected children using health care services at least once during follow-up and the average frequency of attendance in both groups. The risks of being admitted to a hospital ward and of receiving an injection at least once were 2.8 and 2.5 times higher, respectively, in infected than in uninfected children. However, the proportion of children seen at least once in an outpatient clinic did not differ between the two groups. Infected children had significantly more recurrent use of each of the three types of services (1.5–3.5 times) than did uninfected ones.

### Factors Associated With Survival and AIDS Occurrence

An early HIV infection (before 3 months of age) and a short interval (<6 months) between HIV infection and occurrence of the first HIV-related conditions were associated with a poor prognosis (relative hazards of death: 10.3 and 5.4, respectively; Table 3; Fig 2A and 2B). Failure to thrive as the initial pattern of clinical HIV disease tended to be associated with an increased risk of death ( $P = .07$ ). The occurrence of chronic diarrhea, splenomegaly, or chronic parotitis at least once during follow-up was associated with a decrease in the subsequent risk of death (HR: 0.2, 0.3, and 0.1, respectively). The risk of death was

not significantly higher in children who had developed AIDS in comparison to the other children. No specific combination of clinical manifestations was associated with differences in survival (data not shown). Biologically, neither the maternal CD4 cell count at day 15 nor the child's CD4/CD8 ratio at 6 months of age was predictive of death (Table 3).

Clinical AIDS occurred 15 times more frequently in children whose initial pattern of HIV disease included persistent generalized lymphadenopathy (95% CI: 3.1–73.9) and 4.7 times more often in those who presented failure to thrive as the first HIV-related symptom (95% CI: 1.4–16.1; Table 4; Fig 2C). Occurrence of lymphoid interstitial pneumonitis during the course of the disease was associated with a decreased risk of developing AIDS (HR: 0.04; 95% CI: 0.01–0.4) (Table 4; Fig 2D). Age at infection, interval between infection and onset of the first HIV-related conditions, and maternal and children biological characteristics were not associated with the subsequent development of clinical AIDS (Table 4).

### DISCUSSION

This study is the first report describing the long-term natural history of HIV-1 infection from the estimated date of contamination and the prognostic factors in African children followed up prospectively from birth to 5 years of age, compared with uninfected children. The cumulative rate of children lost to follow-up in our cohort was <12% in 5 years and

**TABLE 2.** Use of Health Care Services by 54 HIV-infected Children Compared With 347 Uninfected Children, the Mother-to-Child HIV-1 Transmission Study, Kigali, Rwanda, 1988–1994

Type of Care	Probability of Contact* (95% CI)		HR (Cox) (95% CI)	Recurrence Rate/100 Child-Quarters		RR† (95% CI)
	Infected	Uninfected		Infected	Uninfected	
Outpatient clinic	0.99 (0.94–1.0)	1.0 (0.98–1.0)	0.8 (0.6–1.1)	124.7	84.7	1.5 (1.4–1.6)
Hospital ward	0.8 (0.7–0.9)	0.6 (0.4–0.8)	2.8 (1.9–3.9)	16.5	4.8	3.5 (2.7–4.5)
Medical injections	0.9 (0.8–0.9)	1.0 (0.9–1.0)	2.5 (1.8–3.4)	260.2	100.9	2.6 (2.4–2.7)

\* Kaplan-Meier estimation of the proportion of children using at least once each type of health care services during the first 5 years of life.

† Ratio of recurrence rates (infected/noninfected).

**TABLE 3.** Clinical and Biological Characteristics Associated With Death in 54 HIV-infected Children, the Mother-to-Child Transmission Study Cohort, Kigali, Rwanda, 1988–1994

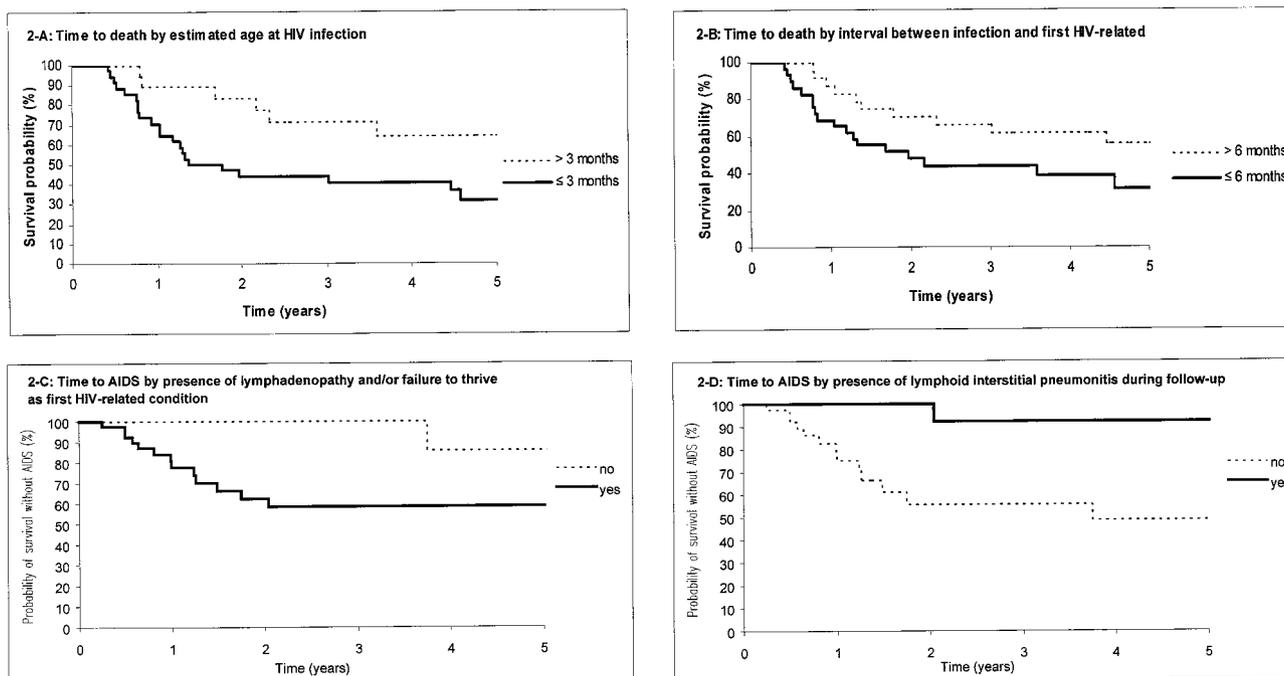
	Number of Children	Number of Deaths	Univariate	Multivariate Analysis	
			<i>P</i>	HR (95% CI)	<i>P</i>
Estimated age at HIV infection					
≤3 months	35	22	.02	10.3 (3.0–34.6)	<.001
>3 months	19	6		1	
First HIV-related signs or symptoms					
Failure to thrive	28	17	.15	2.1 (0.9–4.9)	.07
Lymphadenopathy	24	12	.60		
Oral candidiasis	11	6	.57		
Generalised dermatitis	8	4	.96		
Severe pneumonia	7	5	.18	0.9 (0.2–3.9)	.92
Chronic diarrhea	5	2	.55		
Chronic cough	4	0	.10		
Chronic fever	2	1	.20	0.9 (0.1–9.5)	.95
Hepatomegaly	1	0	1.0		
Splenomegaly	1	0	1.0		
Interval between HIV infection and first HIV-related signs or symptoms					
≤6 months	30	18	.06	5.4 (2.0–14.8)	.001
>6 months	24	10		1	
HIV-related signs/symptoms preceding death					
Failure to thrive	45	25	.34		
Chronic cough	42	21	.29		
Lymphadenopathy	39	16	<.001	0.7 (0.2–2.8)	.60
Hepatomegaly	28	12	.14	1.2 (0.4–3.7)	.73
Generalised dermatitis	25	11	.11	0.8 (0.2–3.0)	.78
Chronic diarrhea	23	8	.007	0.2 (0.1–0.5)	.001
Severe pneumonia	22	11	.39		
Splenomegaly	21	8	.15	0.3 (0.1–0.7)	.01
Lymphoid interstitial pneumonitis	20	7	.01	0.5 (0.1–1.8)	.27
Oral candidiasis	19	12	.37		
Clinical AIDS	14	9	.42		
Chronic fever	11	5	.53		
Chronic parotitis	7	2	.09	0.1 (0.01–0.4)	.003
Maternal CD4 count at day 15					
<350	5	3	.43		
≥350	39	19			
Child CD4/CD8 ratio at 6 months					
<1	21	11			
≥1	21	11	.98		

seems to be particularly low in this African context, strengthening our results. Most published data concerning pediatric HIV infection in developing countries have been either prospective studies that focused primarily on mother-to-child HIV transmission and thus reported limited follow-up of children born to HIV-infected women<sup>13–21</sup> or nonprospective studies focusing on HIV-infected children.<sup>22–26</sup> Thus, despite the large body of information that has been accumulated on mother-to-child HIV transmission, only a few prospective studies, focusing specifically on natural history in HIV-infected children, have been published in developing countries.<sup>27,28</sup> However, such comparative and prospective studies represent the only approach to identify and evaluate the frequency of early and nonspecific clinical or laboratory findings in infected children. This knowledge of early symptomatology may be useful for diagnosis and case management in areas where laboratory facilities are limited, as is often the case in developing countries.<sup>5</sup>

Although clinical patterns of pediatric HIV infection may differ according to the timing of mother-to-child transmission, all infected children of the cohort

were included in our analysis regardless of their estimated date of infection (antenatal, neonatal, or postnatal). Thus, the whole spectrum of vertically acquired pediatric HIV cases, which corresponds with the different patterns of disease routinely encountered in breastfeeding African populations, is considered in this report. In our cohort, morbidity was not different between children infected early in life and other children, but mortality was higher in children in the former group, and analyses were adjusted systematically on timing of transmission to take this variable into account.

The choice of a positive PCR test result as criterion for HIV infection in infants of this cohort was motivated by the ability to estimate the timing of infection by the date of their first positive PCR test result. This may have had an influence on our results: a negative PCR test result at birth may have been compatible with an infection during the neonatal period if viral transmission occurred in the few hours preceding (intrapartum transmission) or following (early postnatal transmission) the test. Therefore, some false-negative results may have occurred leading to the misclassification, at least transient, of in-



**Fig 2.** Kaplan-Meier curves of time to death and AIDS, according to selected covariates in 54 HIV-1-infected children. The Mother-to-Child HIV-1 Transmission Study cohort, Kigali, Rwanda, 1988–1994.

infected children in the uninfected group. Thus, differences between infected and uninfected children may have been underestimated in our analysis.

Our findings first suggest that uninfected children born to seropositive mothers and those born to seronegative mothers do not differ significantly in terms of mortality, morbidity, and use of health care services, although the former children tend to have an increased risk both to develop some defined conditions (ie, severe pneumonia, generalized dermatitis, and chronic parotitis) and to be admitted to the hospital ward. These trends may reflect a consequence of HIV exposure in uninfected children born to seropositive mothers. Considering that our data did not formally prove this potential effect of perinatal HIV exposure, we pooled the two groups of uninfected children in all analyses and compared them as a whole to infected children. We had shown previously, in the same cohort, that HIV-1-uninfected children had similar neonatal anthropometric measurements,<sup>6</sup> the same growth patterns,<sup>29</sup> and comparable neurodevelopmental performances<sup>30</sup> whether they were born to infected or uninfected mothers.

All infected children presented at least one non-specific HIV-related condition in the first 13 months of HIV-1 infection. Although nonspecific findings occurred in both infected and uninfected infants, they were much more common and recurrent among the infected infants. The risk of initial occurrence of chronic cough was not higher in infected than in uninfected children, probably because of its lack of specificity, but chronic cough occurred more recurrently in infected infants. Moreover, these nonspecific features seemed to be more severe in HIV-1-infected children, assessed by the rates of hospital admission and of medical injections that were in-

creased dramatically, compared with uninfected children throughout follow-up. The probability of using outpatient clinic services at least once was very high (nearly 100% for all children), and there was no difference between infected and uninfected subjects (most likely because all of these children were treated free of charge and because even clinic attendance for minor complaints was included). This very high rate of use of medical care services reflects the high quality of follow-up within the cohort.

In HIV-1-infected children, the most frequently observed clinical signs were chronic cough, failure to thrive, and generalized lymphadenopathy, which also were reported among the most frequent HIV-related conditions in other developing countries.<sup>15,16,24,25</sup> Chronic cough and failure to thrive were present in almost half of the initial patterns of symptomatic disease in our series. However, these three conditions were also common in uninfected children. In our cohort, the most specific findings of HIV-1 infection were oral candidiasis and chronic parotitis, a pattern similar to the one observed in the New York City cohort.<sup>31</sup> But in the New York City cohort, failure to thrive and splenomegaly also were reported to be specific symptoms of HIV-1 infection, a difference most likely explained by the higher occurrence of these two symptoms among uninfected children in developing countries.

This study of the progression to AIDS and death among HIV-infected children confirms the probable bimodal clinical expression of the disease. A subgroup of short-term survivors developed severe conditions and died within the first 2 years of life, whereas the rates of mortality and progression to AIDS were lower between 2 and 5 years, suggesting a slower disease progression in children who survived at least 2 years. This bimodal pattern of HIV-

**TABLE 4.** Clinical and Biological Characteristics Associated With AIDS Occurrence in 54 HIV-infected Children, the Mother-to-Child Transmission Study Cohort, Kigali, Rwanda, 1988–1994

	Number Children	Number With AIDS	Univariate	Multivariate Analysis	
			<i>P</i>	HR (95% CI)	<i>P</i>
Estimated age at HIV infection					
≤3 mo	35	9	.58		
>3 mo	19	5			
First HIV-related signs or symptoms					
Failure to thrive	28	10	.07	4.7 (1.4–16.1)	.01
Lymphadenopathy	24	12	.001	15.0 (3.1–73.9)	.001
Oral candidiasis	11	2	.89		
Generalised dermatitis	8	6	<.001	1.0 (0.2–4.7)	.97
Severe pneumonia	7	3	.30		
Chronic diarrhea	5	1	.40		
Chronic cough	4	2	.59		
Chronic fever	2	1	.08		
Hepatomegaly	1	1	<.001		
Splenomegaly	1	1	<.001		
Interval between HIV infection and first HIV-related signs or symptoms					
≤6 mo	30	8	.13	1.0 (0.2–5.5)	.94
>6 mo	24	6			
HIV-related signs/symptoms preceding AIDS occurrence					
Failure to thrive	42	11	.62		
Chronic cough	39	8	.09	0.3 (0.1–1.3)	.11
Lymphadenopathy	35	10	.28		
Hepatomegaly	24	6	.44		
Splenomegaly	19	4	.44		
Generalised dermatitis	17	5	.79		
Severe pneumonia	15	4	.34		
Chronic diarrhea	15	1	.01		
Lymphoid interstitial pneumonitis	14	1	.01	0.04 (0.01–0.4)	.005
Oral candidiasis	13	2	.53		
Chronic fever	7	2	.89		
Chronic parotitis	5	0	.11		
Maternal CD4 count at d 15					
<350	5	1	.87		
≥350	39	11			
Child CD4/CD8 ratio at 6 mo					
<1	21	5	.91		
≥1	21	7			

1-related disease, which has been described previously in American<sup>32</sup> and European<sup>33</sup> HIV-1-infected children, most likely reflects the time when HIV transmission occurs, the infectious dose transmitted by the mother to her offspring, and/or the virulence of the HIV-1 strain.<sup>2</sup> In this report, the association observed between an early estimated age at infection and a shorter survival supports the first of these hypotheses.

The rates of the occurrence of death in HIV-1-infected children (26% at first birthday, 45% at 2 years of age, and 62% at 5 years of age) are close to the rates observed in Uganda and in Zaire in the first 2 years of life<sup>27,28</sup> but are dramatically higher than the rates reported in Brazil and Western countries, where death is estimated to occur in 9% to 16% of the infected children at 1 year of age and 25% to 36% at 5 years of age.<sup>5,31,34–36</sup> The increased mortality in African populations may be explained, at least partly, by the difference in the use of antiretroviral and prophylactic treatments, which have been widespread in industrialized countries and are nonexistent in developing countries. But, because these treatments usually have been prescribed after the child's first birthday, early increased mortality in African

infants is unlikely to reflect the effect of these therapies. The more rapid disease progression in the first year of life also may be caused by a more advanced stage of maternal HIV disease in Africa. However, infected mothers of our cohort did not present clinical or biological signs of advanced disease. Thus, the increased mortality in African HIV-infected children could rather be the witness of a more severe pattern of disease in developing countries, perhaps in relation to multiple and early infectious exposures. The observed rates of progression to AIDS (17% at 1 year of age and 35% at 5 years of age) are close to the rates reported in other cohorts in developing<sup>5</sup> and industrialized countries,<sup>31,34</sup> but the heterogeneity among the studies in the clinical AIDS definitions used (WHO, modified WHO, and Centers for Disease Control and Prevention definitions<sup>37</sup>) makes comparisons difficult to interpret.<sup>5</sup>

Several studies in developing countries<sup>28</sup> and many in industrialized countries<sup>31–33,38,39</sup> have found factors associated with prognosis in HIV-1-infected children. In fact, early onset of HIV-related conditions, failure to thrive, and generalized lymphadenopathy were associated with a poor prognosis, whereas lymphoid interstitial pneumonitis was asso-

ciated with a mild disease. Our data support the significant prognostic value of these conditions, regarding death and/or AIDS occurrence. The failure to thrive and generalized lymphadenopathy had prognostic value, if they occurred as first manifestations of HIV disease, and the occurrence of lymphoid interstitial pneumonitis, at any time during follow-up, was associated with a good prognosis. Chronic diarrhea, splenomegaly, and chronic parotitis also seemed to be associated with a longer survival in this report. These three signs were most likely the witnesses of a chronic HIV disease rather than real prognostic determinants. The absence of the prognostic value of clinical AIDS on survival reflects the inadequacy between the arbitrary definition of AIDS and the clinical disease observed in this African population of HIV-1-infected children, in which no other combination of clinical outcomes was found to have prognostic value. This was probably attributable to the limited sample size.

### CONCLUSIONS

In summary, we found that African HIV-1-infected infants develop disease manifestations early in life and that specific clinical findings are predictive of HIV-1 infection, AIDS, and death. Even if the bimodal evolution that is observed in industrialized countries is confirmed by these data, HIV disease seems to be more severe in developing countries, despite a higher frequency of late acquisition of infection that is related to breastfeeding. This suggests that in addition to the timing of infection other mechanisms may be involved in disease progression. Other cohort data may be useful to confirm these findings and to document morbidity and mortality more thoroughly, especially in the era of antiretroviral therapy. Evaluation of different strategies of prophylaxis of opportunistic infections and case management of the most frequent pediatric HIV-related conditions, adapted to the context of developing countries, are needed to offer adapted and large scale care for HIV-infected children in these countries.

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