

# Predictors of Early Mortality in a Cohort of Human Immunodeficiency Virus Type 1-Infected African Children

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**Background:** Pediatric human immunodeficiency virus type 1 (HIV-1) infection follows a bimodal clinical course with rapid progression in 10–45% of children before the age of 2 years and slower progression in the remainder. A prospective observational study was undertaken to determine predictors of mortality in HIV-1-infected African infants during the first 2 years of life.

**Methods:** Infants in a perinatal cohort identified to be HIV-1-infected by DNA PCR were followed monthly to 1 year, then quarterly to 2 years or death.

**Results:** Among 62 HIV-1-infected infants, infection occurred by the age of 1 month in 56 (90%) infants, and 32 (52%) died at median age of 6.2 months. All infant deaths were caused by infectious diseases, most frequently pneumonia (75%) and diarrhea (41%). Univariate predictors of infant mortality included maternal CD4 count <200 cells/ $\mu$ l [hazard ratio (HR), 3.4;  $P = 0.008$ ], maternal anemia (HR = 3.7;  $P = 0.005$ ), delivery complications (HR = 2.7;  $P = 0.01$ ), low birth weight (HR = 4.1;  $P = 0.001$ ), weight, length and head circumference  $\leq$ 5th percentile at age 1 month (HR = 3.7,  $P = 0.003$ ; HR = 5.8,  $P < 0.001$ ; and HR = 10.4,  $P < 0.001$ , respectively), formula-feeding (HR = 4.0;  $P = 0.01$ ), infant CD4%  $\leq$ 15% (HR = 5.5;  $P = 0.01$ ), infant CD4 count <750 (HR = 9.7;  $P = 0.006$ ) and maternal death (HR = 2.9,  $P = 0.05$ ). In multivar-

iate analysis, maternal CD4 count <200 (HR = 2.7;  $P = 0.03$ ) and delivery complications (HR = 3.4;  $P = 0.005$ ) were independently associated with infant mortality.

**Conclusions:** Advanced maternal HIV disease, maternal anemia, delivery complications, early growth faltering, formula-feeding and low infant CD4 were predictors of early mortality in African HIV-1-infected infants. In resource-poor settings, these predictors may be useful for early identification and treatment of high risk infants.

**Key Words:** Human immunodeficiency virus type 1, disease progression, mortality, predictors

(*Pediatr Infect Dis J* 2004;23: 536–543)

Human immunodeficiency virus type 1 (HIV-1) infection follows a bimodal disease course in vertically infected children with 10–20% and 35–54% of antiretroviral naive children in developed and developing countries, respectively, dying by 2 years of age.<sup>1–5</sup> Children who survive beyond 2 years experience slower disease progression, with a 5-year mortality rate of ~28 and 62% among untreated surviving children in developed and developing countries, respectively.<sup>2,4</sup> The mechanisms behind this difference in pediatric HIV-1 disease progression between developed and developing countries are poorly understood. Potential contributing factors include frequent infectious diseases, quality of immune response, malnutrition, breast-feeding, maternal factors such as advanced disease stage, viral determinants and host genetic factors.

Maternal factors that predict rapid disease progression and/or early mortality among perinatally HIV-1-infected children include low CD4 counts, high viral load (in pregnancy), advanced clinical disease stage, low vitamin A levels during pregnancy and maternal death.<sup>6,7</sup> Infant factors that predict rapid disease progression include early acquisition of HIV, high viral load, early CD4 depletion and early onset of HIV-related symptoms such as growth delay, neurodevelop-

Accepted for publication January 27, 2004.

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Supported by National Institutes of Health grant HD 23412. E.M.O., P.A.O., C.F., and J.O.O. were scholars in the AIDS International Research and Training Program (AIRTP), supported by Fogarty International Center, National Institutes of Health, grant D43-TW00007. D.N., J.O. and G.J.-S. are Scholars of the Pediatric AIDS Foundation.

Presented in part at the Fourteenth International AIDS Conference, Barcelona, Spain, July 7–12, 2002. Abstract ThPeB7219.

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ISSN: 0891-3668/04/2306-0536

DOI: 10.1097/01.inf.0000129692.42964.30

mental delay, hepatomegaly, splenomegaly and lymphadenopathy.<sup>4-6,8-12</sup>

In the absence of HIV-1 infection, breast milk is known to protect against infectious disease and mortality in infancy through provision of passive immunity and nutrition to the infant.<sup>13</sup> It is unclear whether breast-feeding by HIV-1-infected women confers similar protection against infant mortality. Some studies have found that breast-fed HIV-1-infected infants have improved survival, whereas others have found no difference in survival of breast-fed versus non-breast-fed infants.<sup>3,5,14</sup> Because breast-feeding is a pillar of nutrition and survival for children in resource-poor settings, it is important to understand to what extent breast-feeding by HIV-1-infected women improves survival of HIV-1-infected infants.

Care of HIV-1-infected children living in resource-poor settings poses an enormous challenge to the overburdened health care systems in these countries. In a setting in which resources for treatment are limited, early identification of children at high risk of rapid disease progression is important to enable limited resources for HIV-1-specific care to be directed to those who need it most. It is important to have a clear understanding of factors influencing disease progression among HIV-1-infected children in Africa to enable formulation of regionally specific and appropriate guidelines for care of HIV-1-infected children. We prospectively followed a cohort of African children vertically infected with HIV-1 to determine correlates of mortality during the first 2 years of life, specifically evaluating the role of maternal sociodemographic, obstetric and clinical factors, timing of infection, infant nutritional status, immune status and feeding modality.

## MATERIALS AND METHODS

The study participants were HIV-1-infected infants participating in a perinatal cohort study in Nairobi, Kenya. Study subjects were enrolled between November 1999 and June 2002 at a research clinic at the University of Nairobi teaching hospital, Kenyatta National Hospital (KNH). HIV-1-seropositive pregnant women were followed until delivery, given short course zidovudine therapy for prevention of mother-to-child HIV-1 transmission, and after intensive counseling on infant feeding options, allowed to feed their infants as they chose.<sup>15</sup> Severely anemic mothers and mothers intolerant of zidovudine received nevirapine. Infant formula was provided free of charge to mothers who opted not to breast-feed. Transportation costs to the clinic were reimbursed. HIV-1-infected infants were followed monthly during the first year and quarterly during the second year of life. Infants received oral trimethoprim-sulfamethoxazole prophylaxis from the age of 2 months until their HIV-1 infection status was established, after which only HIV-1-infected children continued prophylaxis.<sup>16</sup> All children received free outpatient treatment of illness.

*Study Procedures.* A study physician examined infants within 48 h of birth, at which time gestation was estimated using Dubowitz scores, and venous blood samples were collected. During follow-up, study physicians interviewed mothers on infant feeding and current and intercurrent illness of the child and conducted a physical examination of the child. Patients requiring hospitalization were admitted into KNH and managed by the hospital staff. Cause of death for children who died in KNH was ascertained from hospital clinical records. Autopsies were not performed. Verbal autopsies were conducted to assign a possible cause of death for all children who died outside KNH.

Maternal venous blood samples were collected at 32 weeks gestation for determination of CD4 cell counts and hemoglobin values. Infant venous blood samples (1-3 ml) were drawn within 48 h of birth and at 1, 3, 6, 9 and 12 months of age. Eight drops were placed on filter paper, and the remaining blood was separated into plasma and cells, frozen and stored. Once an infant was known to be HIV-1-infected, 0.5 ml of all subsequent venous blood samples was used for CD4 cell count determination.

*Laboratory Methods.* For determination of infant HIV-1 status, nested HIV-1 DNA PCR was used to amplify HIV-1 gag sequences from dried blood spots on filter papers. Quadruplicate PCRs were performed on the same blood spot, and the sample was considered positive if  $\geq 1$  of 4 PCRs were positive. This test has a sensitivity and specificity of 96 and 100%, respectively.<sup>17</sup> Infants were defined as HIV-1-infected if they had 2 consecutive positive HIV-1 DNA PCR test results or 1 positive result if the sample was obtained at the last infant visit.

Quantitative analysis of plasma HIV-1 RNA was conducted with a transcription-mediated amplification (TMA) method developed by GenProbe which is sensitive for detection of Kenyan HIV-1 subtypes A, C and D.<sup>18</sup> To determine precise timing of infection, HIV-1 RNA TMA assays were conducted on all available infant samples from the visit before the first detection of HIV-1 DNA. Timing of HIV-1 infection was defined by the earliest positive HIV-1 DNA PCR or RNA TMA result.

Total white blood cell counts, lymphocyte differential count and percentage of CD4 and CD8 lymphocytes were determined using FACScan flow cytometry (BD Biosciences, Mountain View, CA).

*Statistical Analysis.* All data was analyzed with SPSS 10.0 for Windows (SPSS, Inc., Chicago, IL). HIV-1-infected infants were categorized into survivors and nonsurvivors. Analyses were restricted to infants who had at least 6 months of follow-up after HIV-1 infection, to provide sufficient follow-up data. To determine predictors of mortality, univariate and multivariate Cox proportional hazards regression models were performed, with time from first HIV-1-positive test result to death as outcome. For analyses of mode of feeding

as a correlate of mortality, survival to age 6 months was evaluated among infants infected perinatally and in utero, given that breast-feeding is most protective against mortality during the first 6 months of life.

Specific variables were categorized before inclusion in the statistical models. Infants were classified into those with early HIV-1 infection (first positive HIV-1 PCR test by the age of 1 month) and late infection (negative test at the age of 1 month followed by a positive test); breast feeders and formula feeders (ever versus never breast-fed). Among infants who survived to age 6 months, CD4 count and percentage at age 6 months was evaluated as a predictor of subsequent survival. Severe immunosuppression among infants was defined as CD4% of  $\leq 15\%$ . Mothers were classified according to prenatal CD4 count into those with (CD4  $< 200$  cells/ $\mu$ l) and without (CD4  $\geq 200$  cells/ $\mu$ l) severe immunosuppression.

Factors that were significantly associated with infant mortality in univariate analyses and for which data were available in all 62 infants were included in multivariate models. If 2 or more factors were correlated (such as anthropometric measurements weight, height and head circumference, or maternal CD4 count and maternal death), one measurement was selected to represent other correlated factors in the multivariate model.

Infant mortality rates among the HIV-1-exposed uninfected children in the parent cohort were determined to provide baseline data against which survival of HIV-1-infected infants could be compared.

## RESULTS

### Cohort Characteristics

Sixty-two HIV-1-infected infants were included in this analysis. Their mothers were a median age of 25 years and had received a median of 8 years of education; 49 (79%) lived in 1-room houses (Table 1).

During pregnancy, 46 (75%) women took zidovudine prophylaxis for a median duration of 3 weeks. Reasons for not taking zidovudine prophylaxis included premature delivery ( $n = 6$ ), incorrect estimation of last menstrual period ( $n = 8$ ) and severe anemia in third trimester (hemoglobin  $< 8$  g/dl,  $n = 3$ ). Nevirapine was administered during labor to the mother and within 72 h to the infant if the mother had not initiated zidovudine therapy.

Six (10%) women had hemoglobin  $< 8$  g/dl in pregnancy, 9 (15%) had membrane rupture more than 4 h before delivery, 52 (84%) delivered their infant vaginally and 10 (16%) underwent emergency cesarean section after labor onset. Median labor duration was 8 h for vaginal deliveries and 14 h for women who eventually underwent emergency cesarean section. The median CD4 count among mothers during the third trimester of pregnancy was 377 cells/ $\mu$ l, and

**TABLE 1.** Description of the Cohort of HIV-1-Infected Children

Characteristic	Median Value or Frequency (%)	N*
Maternal sociodemographic characteristics		
Median maternal age (yr; range)	25 (18–38)	61
Median maternal years of education (range)	8 (0–14)	62
Median parity (range)	3 (1–8)	62
No. living in 1-room house (%)	49 (79)	62
No. married (%)	51 (82)	62
Obstetric and maternal clinical characteristics		
No. receiving antenatal zidovudine (%)	46 (75)	61
No. with hemoglobin $< 8$ g/dl in pregnancy (%)	6 (10)	62
No. with rupture of membranes $> 4$ h (%)	9 (15)	62
No. with vaginal delivery (%)	52 (84)	62
Median maternal CD4 count (cells/ $\mu$ l; range)	377 (6–880)	62
Median body mass index 1 mo postpartum (range)	22 (17–28)	55
Maternal deaths (%)	5 (8)	62
Infant characteristics		
Median gestational age (wk; range)	39 (33–42)	54
Median birth wt (kg; range)	3.0 (1.9–4.0)	61
Median Apgar score at 10 min (range)	10 (9–10)	53
No. breast-fed from birth (%)	51 (82)	62
No. female (%)	33 (53)	62
No. with early HIV-1 infection $\leq 1$ mo of age (%)	56 (90)	62
Median CD4 count at age 6 mo (cells/ $\mu$ l; range)	1262 (165–3692)	28
Median CD4% at age 6 mo (range)	21 (3–40)	28
No. of infants lost to follow-up (%)	5 (8)	62
No. of infant deaths (%)	32 (52)	62
Median age at death (mo; range)	6.2 (1.3–24.5)	31
Median follow-up duration among survivors (mo; range)	17 (6–26)	30

\*Number of infants for whom data on this characteristic were available.

10 (16%) had CD4 count  $< 200$  cells/ $\mu$ l. Median body mass index at 1 month postpartum was 22 kg/m<sup>2</sup>. Five (8%) mothers died during the study.

The infants were born at a median gestation of 39 weeks, had a median birth weight of 3.0 kg and had a median Apgar score of 10 at 10 min after birth. Thirty-three (53%) infants were female, and 51 (82%) ever breast-fed. There was 1 twin delivery in the cohort; only the firstborn twin is included in this analysis.

HIV-1 infection was diagnosed by the age of 1 month in 56 (90%) infants and after 1 month in the remaining 6 (10%). Forty-three (96%) of 45 infants took trimethoprim-sulfamethoxazole prophylaxis, and 31 demonstrated good compliance (adherence  $> 75\%$  of the time). Death occurred in 32 (52%) of 62 infants during the 2-year follow-up period; 25 (40%) died during the first year, and 7 (12%) died during the second year of life. One year mortality risk after Kaplan-Meier survival analysis was 44.5%. Median age at death was 6.2 months (range, 1.3–24.5 months). In contrast, among 311 HIV-1-uninfected infants in the parent cohort, the 1-year

mortality rate was 10.0%, and median age at death was 2.4 months (range, 2 days–6.8 months). Comparison of 1-year mortality between HIV-1-infected and -uninfected infants showed 4-fold increased mortality among the former [hazard ratio (HR), 4.0; 95% confidence interval (CI) 2.1–7.6;  $P < 0.001$ ]. Among HIV-1-infected infants who were alive at the end of follow-up, median follow-up time was 17 months. Five infants (8%) were lost to follow-up during the study.

Data were available on CD4 counts and CD4% at the age of 6 months for 28 (60%) of 47 HIV-1-infected infants who were alive at this age and infected before 3 months of age. These infants had a median CD4 count of 1262 cells/ $\mu$ l and a median CD4% of 21%. Eight (29%) of 28 infants had CD4%  $\leq$ 15% at age 6 months.

### Cause of Death

Infectious disease was responsible for all 32 deaths in this HIV-1-infected cohort of children. The most frequent infectious disease was pneumonia, present in 24 (75%) of 32 children at time of death, followed by diarrhea in 13 (41%), sepsis in 4 (13%) and meningitis in 4 (13%) (Table 2). Failure to thrive was also a frequent contributing factor to death and was evident in 20 (63%) children during the months preceding death. More than 1 potential contributing cause of death was present for 23 children. Of 21 children for whom CD4 data were available before death, 19 were immunosuppressed (CD4  $<$  25%). Twenty-two (69%) of the 32 infants who died were hospitalized at least once during follow-up.

Among uninfected children in the parent cohort who died, cause of death was similar to that of the HIV-1-infected children, with the most frequent contributory causes of death being pneumonia followed by diarrhea.

### Correlates of Infant Mortality

**Maternal and Obstetric Factors.** Infants whose mothers had prenatal CD4 counts of  $<$ 200 cells/ $\mu$ l had a 3-fold increased mortality risk compared with infants whose mothers had CD4 counts of  $\geq$ 200 cells/ $\mu$ l ( $P = 0.007$ ) (Table 3). Median survival of infants born to mothers with a CD4 count of  $<$ 200

cells/ $\mu$ l was 5.7 months (95% CI 2.1–9.4 months) compared with 19.9 (95% CI 13.0–26.7) months for infants of mothers with CD4  $\geq$ 200 cells/ $\mu$ l (Fig. 1). Maternal death was associated with a 3-fold increased risk of infant death ( $P = 0.05$ ). Maternal age, education, marital status, parity, nutritional status (body mass index), socioeconomic status (as measured by number of rooms in residence) and zidovudine prophylaxis in pregnancy were not predictive of infant mortality in this cohort ( $P > 0.05$ ).

There was increased infant mortality if a mother had hemoglobin  $<$ 8 g/dl during the third trimester (HR = 3.7;  $P = 0.005$ ). Infants born by emergency cesarean section had a 3-fold increased risk of death compared with infants born vaginally ( $P = 0.01$ ).

**Infant Factors.** Low birth weight infants ( $<$ 2.5 kg) experienced higher mortality than infants of normal birth weight (HR = 4.1;  $P = 0.001$ ). No association was found between prematurity (Dubowitz estimation  $<$ 37 weeks) or early timing of HIV-1 infection and mortality in this cohort. However, because of the small number of children born prematurely and few with late acquisition of HIV-1, we had limited statistical power to evaluate these particular factors. In this cohort, infants who were never breast-fed were more likely to die before 6 months of age than infants who breast-fed (HR = 4.0; 95% CI 1.4–11.5;  $P = 0.01$ ). Mean age at death of the 7 non-breast-fed infants who died was 3.2 months, whereas among the 25 breast-fed infants who died mean age at death was 9.6 months. All deaths among non-breast-fed infants occurred during the first 6 months of life. In addition, non-breast-fed infants were more likely to be of low weight for age at age 1 month than breast-fed infants (4 of 11 non-breast-fed infants compared with 4 of 51 breast-fed infants had weight  $\leq$ 5th percentile for age at 1 month;  $P = 0.03$ ).

Infants with weight, length and head circumference below the 5th percentile for age at 1 month of age were more likely to die than infants of normal anthropometric parameters at this age (HR  $>$  3.0;  $P <$  0.005). To determine whether this association was independent of prematurity, this analysis was repeated, this time restricting it to full term infants (born at  $\geq$ 37 weeks gestation;  $n = 45$ ). Weight and length  $\leq$ 5th percentile at age 1 month remained predictive of increased mortality risk among full term infants ( $P <$  0.03). All infants with low weight and/or low height for age at 1 month were also HIV-1-infected by that age. Only one full term infant had a small head circumference at age 1 month; therefore this could not be evaluated as a predictor of mortality among full term infants.

Among infants who were HIV-1-infected and alive at the age of 6 months, CD4%  $\leq$ 15% and absolute CD4 count  $<$ 750 were predictive of mortality before age 2 years (HR = 5.7;  $P = 0.01$  and HR = 9.7;  $P = 0.006$ , respectively) (Table 3). Mean survival of infants with CD4%  $\leq$ 15% at age 6 months was 14.2 months (95% CI 7.5–20.9 months) compared with 22.6 (95% CI

**TABLE 2.** Potential Contributing Causes of Death\* ( $N = 32$ )

Potential Contributing Cause of Death	No.
Pneumonia	24 (75) <sup>†</sup>
Failure to thrive	20 (63)
Diarrhea	13 (41)
Sepsis	4 (13)
Meningitis	4 (13)
Anemia	4 (13)
Measles	2 (6)
Malaria	1 (3)
Tuberculosis	1 (3)
Ricketts	1 (3)

\*More than 1 potential contributing cause of death was present for 23 children.

<sup>†</sup>Numbers in parentheses, percent.

**TABLE 3.** Predictors of Infant Mortality: Univariate Analysis

Risk Factor	Mortality Incidence*		Hazard Ratio	P
	With Risk Factor	Without Risk Factor		
<b>Maternal factors, obstetric and clinical</b>				
Zidovudine prophylaxis during pregnancy	47	68	0.9 (0.8–1.1) <sup>†</sup>	0.31
Hemoglobin <8 g/dl in 3rd trimester	176	46	3.7 (1.5–9.3)	0.005
Prolonged rupture of membranes (>4 h)	35	56	0.6 (0.2–2.0)	0.43
Emergency C/S vs vaginal delivery	119	44	2.7 (1.2–5.9)	0.01
Body mass index below median <sup>‡</sup>	49	45	1.1 (0.5–2.5)	0.79
CD4 count <200 cells/ $\mu$ l	159	45	3.4 (1.4–8.5)	0.007
Maternal death	147	49	2.9 (1.0–8.5)	0.05
<b>Infant factors</b>				
<b>Perinatal</b>				
Low birth (wt $\leq$ 2.5 kg)	164	43	4.1 (1.7–9.8)	0.001
Prematurity (gestational age <36 wk)	86	49	1.8 (0.7–4.9)	0.22
Early vs late HIV-1 infection	53	43	1.1 (0.3–3.8)	0.83
Formula-fed vs breast-fed <sup>§</sup>	103	47	4.0 (1.4–11.5)	0.01
<b>Clinical</b>				
Low wt for age $\leq$ 5th percentile <sup>¶</sup>	166	45	3.8 (1.6–8.9)	0.002
Low length for age $\leq$ 5th percentile <sup>¶</sup>	219	40	5.8 (2.6–13.0)	<0.001
Low head circumference for age $\leq$ 5th percentile <sup>¶</sup>	420	47	10.4 (3.2–33.1)	<0.001
CD4% at 6 mo $\leq$ 15%	68	14	5.7 (1.5–21.6)	0.01
CD4 count at 6 mo < 750 cells/ml	84	19	9.7 (1.9–49.7)	0.006
Drop in CD4% during follow-up >10%	46	17	3.0 (1.2–7.1)	0.02

\*Mortality incidence = number of deaths per 100 person-years at risk.

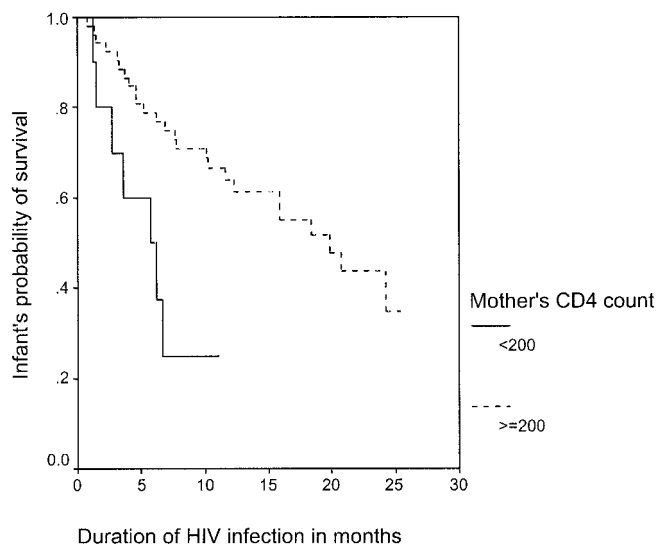
<sup>†</sup>Numbers in parentheses, 95% CI.

<sup>‡</sup>BMI measured at 1 month postpartum.

<sup>§</sup>Analysis restricted to survival during the first 6 months of life.

<sup>¶</sup>Anthropometric measurements at the age of 1 month.

C/S, Cesarean section.



**FIGURE 1.** Kaplan-Meier survival curves of 62 HIV-1-infected infants during the first 2 years of life, according to maternal CD4 count during pregnancy. Log rank statistic, 8.20;  $P = 0.005$ .

20.1–25.1) months for infants with CD4% >15% at age 6 months (Fig. 2). Among 42 infants for whom CD4 measurements were available at 2 or more time points, a decline in

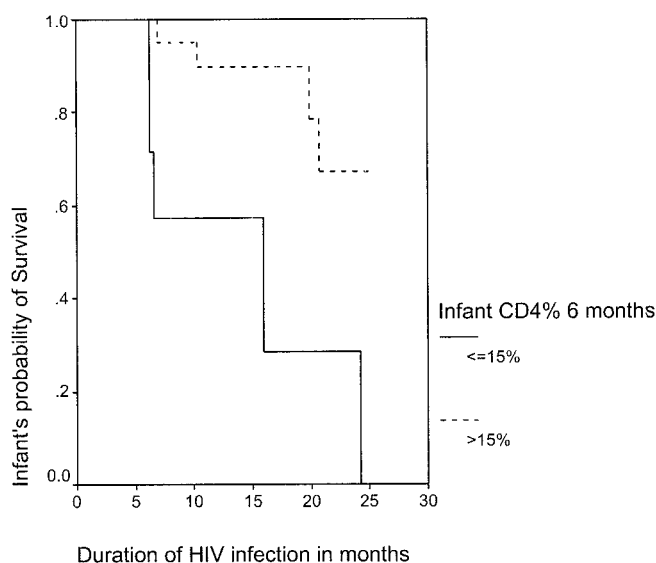
CD4% of >10% during follow-up was associated with 3-fold increased risk of early death ( $P = 0.02$ ).

### Multivariate Analysis

Maternal CD4 count, mode of delivery, mode of feeding and weight percentile at the age of 1 month were included in the multivariate model to evaluate independent correlation with infant mortality (Table 4). As a result of the correlation among weight, length and head circumference, only one anthropometric measurement was included in the model. Maternal CD4 count and maternal death were correlated; therefore maternal CD4 count was included in the model as an indicator of maternal disease stage. In adjusted analysis, severe maternal immunosuppression (HR = 2.7;  $P = 0.03$ ) and emergent cesarean section delivery (HR = 3.4;  $P = 0.005$ ) were independently predictive of early infant mortality in this cohort. Formula-feeding ( $P = 0.08$ ) and low weight for age at 1 month ( $P = 0.11$ ) showed a trend for association with early infant mortality.

### DISCUSSION

The rapid disease progression and high mortality seen in this cohort of HIV-1-infected children underscores the highly aggressive nature of pediatric HIV in sub-Saharan Africa, as reported in earlier African cohorts.<sup>3–5,9,19</sup> This mortality (~44.5% at 1 year) far exceeds the current Kenyan infant mortality rate of 7.6% and the infant mortality rate of HIV-1-uninfected children (10.0%) born to mothers in the



**FIGURE 2.** Kaplan-Meier survival curves of 28 infants HIV-1-infected by 1 month of age, according to CD4% at age of 6 months. Log rank statistic, 7.95;  $P = 0.005$ .

**TABLE 4.** Predictors of Infant Mortality\* Multivariate Analysis

Correlate (N = 62)	Hazard Ratio	P
Maternal CD4 count vs $\geq 200$ cells/ $\mu$ l	2.7 (1.1–6.9)*	0.03
Formula-fed vs breast-fed	2.3 (0.9–6.0)	0.08
Emergency C/S vs vaginal delivery	3.4 (1.5–8.0)	0.005
Wt for age percentile at age 1 mo	1.0 (1.0–1.0)	0.11

\*Numbers in parentheses, 95% CI.  
C/S, Cesarean section.

same cohort.<sup>20</sup> During the past decade, infant and child mortality in Kenya has increased as a result of pediatric HIV-1.<sup>21</sup> Thus, continued expansion of programs to prevent infant HIV-1 infection remain an urgent priority.

Despite high uptake and compliance with trimethoprim-sulfamethoxazole prophylaxis and provision of outpatient care, 2-year mortality in this cohort was surprisingly similar to mortality reported from previous cohort studies in infants who did not receive prophylaxis.<sup>5</sup> We speculate that the benefit of trimethoprim-sulfamethoxazole may have been offset by predominantly early timing of HIV-1 infection in this cohort (90% of infants were diagnosed before 1 month of age) because of shortened breastfeeding practices. In our previous Nairobi cohort of HIV-1-infected children, infants diagnosed before the 2nd month of life experienced higher 2-year mortality (63%) than infants diagnosed later (8%;  $P < 0.001$ ).<sup>5</sup>

Our data suggest that several factors contribute to rapid infant HIV-1 disease progression including advanced maternal disease (CD4 < 200 and maternal death), maternal

anemia, low birth weight, early growth faltering, not breastfeeding and delivery complications.<sup>6,7,19</sup> Various biologic and psychosocial mechanisms may explain why advanced maternal disease is associated with rapid infant disease progression. Mothers with AIDS may transmit more virulent virus, with consequent high replication and rapid CD4 depletion in the infant, a phenomenon that has been demonstrated in animal models.<sup>22–24</sup> Immune function in immunocompromised mothers is reduced, and infants born to such mothers may receive inferior passive immunity (transplacentally and/or from breast milk), increasing their susceptibility to infectious disease.<sup>25–27</sup> In addition, mothers with AIDS may be less able to give quality care to their infants because of frequent illness and reduced well-being. Thus exposure to virus in high dose or of high virulence, inadequate passively acquired immunity and poor maternal care may act synergistically to lead to rapid disease progression.

In this study, infants delivered by emergent cesarean section experienced worse long term outcome than infants delivered vaginally. All infants had good Apgar scores at birth and survived beyond the first month of life, suggesting that the observed mortality was not caused by birth injury. Median duration of labor was longer for emergent cesarean section than for vaginal deliveries, possibly exposing infants to higher infective dose of virus and leading to more rapid disease progression. This finding underscores the fact that quality of obstetric care not only impacts immediate pregnancy outcome but can also impact the long term survival of infants who become HIV-1-infected perinatally. Priority must be given to improving quality of obstetric care in this region.

Early growth faltering identified HIV-1-infected infants who are likely to have rapidly progressive disease. The association between growth faltering and infant mortality was less strong after adjustment for maternal CD4 count, suggesting that growth faltering is in the causal pathway between advanced maternal disease and infant mortality. All infants with early growth faltering were HIV-1-infected either in utero or perinatally, suggesting that their poor growth may have been a marker of disease progression. Our data complement the findings of others who have found a relationship between suboptimal growth and survival of HIV-1-infected infants.<sup>3,4,9,28–30</sup> Factors that have been shown to influence growth during this period include viral burden, increased metabolic requirements during infection and neonatal nutrition.<sup>31–34</sup> Growth monitoring is routine and may provide a useful indicator for further diagnostic and treatment decisions.

We found that breast-feeding was protective against mortality during the first 6 months of life in this cohort of HIV-1-infected children. This is consistent with some but not all studies in HIV-1-infected children.<sup>13,14,35</sup> Possible mechanisms through which breast milk improved outcome include superior nutrition, better bonding leading to better quality of

care and passive immune protection. Formula-fed infants were more likely to exhibit growth delay during the first month of life than breast-fed infants, despite being provided with free infant formula. Our finding corroborates the finding of the earlier Nairobi breast-feeding study where formula-fed infants experienced higher mortality during the first 6 weeks than breast-fed infants.<sup>35</sup> This implies a delicate balance between the benefits (reduced HIV-1 transmission) and risks (increased mortality) from formula feeding. These findings also suggest that as HIV disease progresses in latter infancy, factors other than mode of feeding become the major determinants of survival. By 1 year, formula feeding was not associated with adverse risk in either study. Our current study had several differences from the first: (1) the study design was observational; (2) feeding choice was self-selected rather than randomized; and (3) women received zidovudine and infants received trimethoprim-sulfamethoxazole prophylaxis. From our current study, we can conclude that among women whose infants are HIV-1-infected and formula-fed, there should be intensive monitoring to prevent mortality during the first 6 months of life.

Among infants infected early who survived to the age of 6 months, severe immunosuppression (CD4%  $\leq$ 15% or CD4 count <750 cells/ml) was predictive of early mortality as has been seen in western cohorts.<sup>6,10,11,36</sup> Our findings suggest that in African HIV-1-infected infants absolute CD4 count and CD4% are useful prognostic measures and may guide decisions regarding opportunistic infection prophylaxis and initiation and monitoring of antiretroviral therapy.<sup>37</sup>

We have determined several correlates of mortality in this African cohort of children with vertically acquired HIV-1 infection. We observed that advanced maternal disease in pregnancy, maternal anemia, delivery complications, maternal death, early growth faltering, non-breast-feeding and development of severe immunosuppression before 6 months of age predicted mortality before the age of 2 years. In resource-poor settings, several of these correlates may be used to identify HIV-1-infected infants who are at high risk of rapid disease progression and to determine which infants should be prioritized for early antiretroviral treatment. Our findings also suggest that delaying maternal disease progression may positively impact the survival of perinatally infected children and underscores the need for care programs to incorporate highly active antiretroviral therapy and opportunistic infection prophylaxis for both mothers and infants.

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