Growth Failure as a Prognostic Indicator of Mortality in Pediatric HIV Infection

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ABSTRACT. *Objective.* To study the effect of perinatally acquired human immunodeficiency virus (HIV) on somatic growth and examine the relationship of nutritional status to mortality in HIV-infected infants.

Method. Pregnant women attending the antenatal clinic at Mulago hospital in Kampala, Uganda, were enrolled. All live-born babies born to HIV-1 seropositive (HIV+) women, and to every fourth age-matched HIV-1 seronegative (HIV−) woman, were followed for 25 months.

Results. The mean weight-for-age and length-for-age curves of HIV+ children were significantly lower than those of HIV− controls and seroeverters. Forty-five (54%) of the 84 HIV+ infants died before their second birthday, as compared with a 1.6% and 5.6% mortality in HIV− and seroeverters. HIV+ infants with an average weight-for-age Z-score below −1.5 in the first year of life have a nearly fivefold risk of dying before 25 months of age compared with noninfected controls.

Conclusion. Perinatally acquired HIV infection is associated with early and progressive growth failure. The severity of growth failure is associated with an increased risk of mortality. The effect of early, aggressive nutritional intervention in delaying HIV progression and mortality should be evaluated by controlled intervention studies. *Pediatrics* 1997;100(1). URL: http://www.pediatrics.org/cgi/content/full/100/1/e7; *HIV-1, mortality, weight-for-age Z-score, height for age Z-score.*

ABBREVIATIONS. HIV, human immunodeficiency virus; EIA, enzyme immunoassay; PCR, polymerase chain reaction; ICD, immune complex dissociation; WAZ, weight-for-age Z-scores; GEE, generalized estimating equations; AIDS, acquired immune deficiency syndrome.

Several studies have reported growth failure in children with perinatally acquired human immunodeficiency virus (HIV) infection.[1–5] The onset of growth failure has been variable. Some studies have reported growth deceleration as early as the first few months of life[1,2] and others have shown normal growth rates well into the second year of life.[3] However, these studies were retrospective, involved a small number of subjects and included confounding factors such as infants of drug-addicted mothers and infants on retroviral therapy. In addition, although malnutrition is generally recognized as a risk factor for child mortality, the role of nutritional status in disease progression of HIV and in related mortality has not been studied in a prospective manner.

We followed HIV+ children, control groups of seroeverters and infants born to HIV− mothers with serial weight and length measurements until their second birthday. Growth patterns and the relationship of nutritional status to mortality were analyzed.

PATIENTS AND METHODS

Study Patients

Pregnant women attending the antenatal clinic at Mulago hospital in Kampala, Uganda from 1990–1992 were enrolled in a study of HIV-1 infection in pregnancy sponsored by the World Health Organization in collaboration with the Department of Obstetrics and Gynaecology at Makerere University Medical School in Kampala. Women were eligible for the study if they were less than 28 weeks gestation, lived within 15 km of the hospital, were willing to be tested for HIV-1 and were willing to deliver at Mulago Hospital. All live-born infants born to HIV+ mothers and to every fourth age-matched HIV− mother were enrolled in the pediatric studies. The overall HIV-1 seroprevalence rate of pregnant women was 28%. Five hundred twenty term infants were enrolled in the study. The children did not receive zidovudine or any other antiretroviral agent at any point during follow-up.

HIV Status

Blood was obtained from study infants at birth, 6 weeks, 6 months, 12 months and ≥15 months. HIV-1 status was determined by HIV-1 enzyme immunoassay (EIA) at ≥15 months in surviving infants with confirmatory Western blots of all seropositives. Western blots were considered positive if they contained any two of the following HIV-1 specific bands: gp160/120, gp41 or p24.[6] Patients were classified as HIV Infected (HIV+) if both the mother and infant were positive by both EIA and Western blot techniques. HIV-1 DNA polymerase chain reaction (PCR) and immune complex dissociation (ICD) p24 antigen testing were performed on specimens from children who were lost or had died before 15 months of age. Of the 84 children who were found to be HIV+, 49 had a positive serology based on EIA and Western blot at or beyond 15 months of age. Of the remaining 35, 29 were positive by more than one early diagnostic test (p24 and PCR). Three were based on PCR alone and three were based on ICD p24 antigen testing alone. ICD p24 was never used as the sole criterion in infants less than 1 month of age. Infants who were born to HIV+ mothers but were seronegative were classified as seroeverters.

Infants who were born to HIV-negative (HIV−) mothers and were themselves negative were classified as HIV−.

Anthropometric Measurements

Birth weight was obtained from delivery room records and length measured by pediatrician at the time of first visit. Subsequent anthropometric measurements were performed by two experienced nurses trained in standard anthropometric techniques. Measurements were scheduled to be taken every month up to 3 months of age and every 3 months thereafter until 2 years of age. Subjects were weighed unclothed on a hanging Salter scale. Length was measured in a recumbent position using a length board stadiometer. All measurements from birth to 25 months of age were included in the analysis.

Statistical Analysis

Data were entered using the EPI-INFO program (Centers for Disease Control and Prevention, Atlanta, GA), which was also used to compute weight-for-age Z-scores (WAZ). The weight-for-age Z-score represents the number of standard deviations above/below the median weight for a reference population at that age.[7,8] Analysis was performed using SAS.[9] The generalized estimating equation (GEE) approach was used to model longitudinal weight and length data. This regression method can analyze data sets with a variable number of measurements per individual and takes into account the correlation between repeated measurements on the same child.[10,11] After an exploratory phase, the regression model (see Fig 1 and Fig 2) was chosen to be a 6-parameter cubic spline with knots at 6 and 12 months.[12] In the GEE analysis, robust variance estimates and the exchangeable working correlation matrix were used. Fisher's exact test was used to test for differences in mortality and for the association between nutritional status and mortality. Analysis of variance was used to compare birth weights and lengths.

RESULTS

Five hundred twenty infants were followed prospectively from birth. Eighty-four (16.2%) of the children were HIV+. One hundred twenty-four (23.8%) of the children were negative. Two hundred fifty-one (48.3%) were seroeverters.

Sixty-one children (11.7%) were unclassified and were excluded from the analysis. The unclassified group consisted of 35 infants who were born to HIV+ mothers but had equivocal results, 11 who were HIV− born to mothers who had equivocal HIV results, 7 with equivocal HIV results born to mothers who are negative, and 8 infants born to mothers who did not have Western blot testing to confirm HIV positivity.
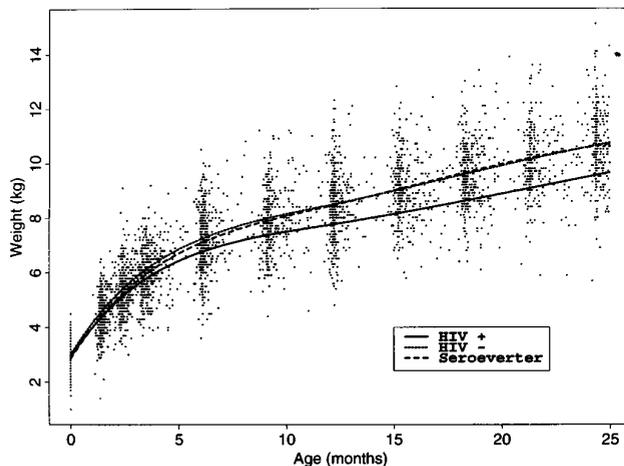

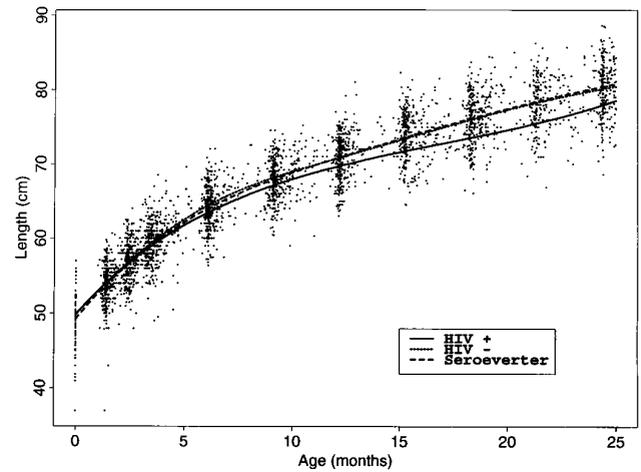**Fig 1.** Mean weight-for-age in HIV+, HIV−, and seroeverter infants.

Fig 2. Mean length-for-age in HIV+, HIV−, and seroeverter infants.

Of the 459 patients with known HIV status, 51.9% were male and 48.1% were female. A total of 3820 weight measurements and 3811 length measurements were available for ages 0 to 25 months (mean of 8.3; range 1–11 measurements/child). Apgar scores, Dubowitz scores, gender, socioeconomic status, duration of breastfeeding, and ethnic background were not different between HIV+ infants, seroeverters and HIV− controls.

The distribution of birth weight and length in the three groups is shown in Table 1. Mean weight-for-age and length-for-age curves for each of the three groups are as shown in Figs 1 and 2. The three weight-for-age curves are significantly different ($P <$ .0001). The weight-for-age curve for HIV+ children differs significantly from that of HIV− controls and of seroeverters ($P = $ .0012 and $P <$ .0001, respectively). At 6 months of age, HIV+ children had a significantly lower mean weight than both HIV− and seroeverters ($P = $ .004 and $P = $ .027). Similarly, (see Fig 2), differences are noted in the length-for-age curves between HIV+, HIV− and seroeverters ($P <$ .0001). Growth differences between the three groups

TABLE 1. Birth Weight and Length (mean ± SD), in HIV-positive, HIV-negative, and Seroeverter Ugandan Infants

	Birth Weight (kg)	Birth Length (cm)
HIV-positive	2.97 ± 0.53	49.97 ± 3.14
HIV-negative	3.03 ± 0.49	49.95 ± 2.50
Seroeverters	2.87 ± 0.44	49.34 ± 2.37

Seroeverters had a lower birth weight and length; $P = $ .047, .051, respectively.

TABLE 2. Mortality Distribution of Infants Born to HIV-Infected Women by Infant's HIV Status at Mulago Hospital, Uganda (1990–1992)

Age at Death	HIV-positive	HIV-negative	Seroeverters
0–<6 months	13 (15.5%)	⋯	⋯
6–<12 months	12 (14.3%)	⋯	5 (2.0%)
12–<18 months	9 (10.7%)	2 (1.6%)	7 (2.8%)
18–<25 months	11 (13.1%)	⋯	2 (0.8%)
≥25 months (alive by 25 months)	39 (46.4%)	122 (98.4%)	237 (94.4%)

TABLE 3. Association Between Average Weight-for-Age in the First Year of Life and Mortality by 25 Months for HIV-positive Infants at Mulago Hospital, Uganda (1990–1992)

Average WAZ in First Year of Life	Mortality Rate	Mortality Odds Ratio (95% CI)	P Value
Below −0.75	26/39	2.74 (1.12–6.67)	.030
Above −0.75	19/45		
Below −1.0	21/29	3.39 (1.28–8.97)	.021
Above −1.0	24/55		
Below −1.5	13/16	4.87 (1.27–18.67)	.024
Above −1.5	32/68		

persist even when children with early mortality (death before 25 months of age) are excluded (data not shown).

Sixty-one patients died during the period of observation. Table 2 shows the distribution of mortality by group and age at death. Forty-five of 84 HIV+ infants (54%) died before their second birthday, a significantly higher proportion than of HIV− controls and seroeverters (both P < .0001). Among the HIV+ infants, those with an average weight-for-age Z-score below −1.5 over the first year of life have a nearly fivefold odds of dying before 25 months of age compared with those with WAZ more than −1.5 (Table 3). Low weight-for-age Z-scores in the first 6 months of life were also associated with increased mortality rate by 25 months of age.

DISCUSSION

Our analysis demonstrates that perinatally acquired HIV infection is associated with early and progressive decrements in weight and length. The differences in weight and length between the HIV+ children and controls persisted even when patients who died before 25 months of age were removed from analysis. This finding is consistent with findings from other studies[1] and suggests that this relationship is not totally caused by a subpopulation of very ill children.

Almost half of the HIV+ children died before 25 months of age, as compared with only 5.6 and 1.6% of seroeverters and negatives respectively. This mortality rate is consistent with reports from Haiti and Zaire[13,14] but is much higher than mortality rates reported from Europe and North America, where median survival of about 4 years of age are reported.[15,16] The poor outcome in the HIV+ infants cannot all be attributed to poverty and underdevelopment, because the control groups shared the same socioeconomic environment.

Our data show a striking inverse association between early nutritional status and mortality risk. The association between nutritional status and mortality is consistent with findings in a Rwandan cohort[17] where an inverse association between nutritional status at 12 months of age and mortality by the second birthday was demonstrated. Similar findings were also reported in a US study which found weight below the third percentile to be a relatively specific (93%), although not sensitive (31%) predictor of mortality.[18]

The strong association between poor growth and mortality suggests two possible mechanisms. First, poor nutritional parameters may represent the general debilitation of infants with frequent opportunistic infections who eventually succumb and die. The association of infection-induced cachexia to mortality has been well documented in adult acquired immune deficiency syndrome (AIDS) patients[19] and is probably induced by the effect of recurrent infections on food intake, absorption and energy expenditure.[20–22]

An alternative possibility is that poor nutritional status accelerates the progression from asymptomatic HIV infection to AIDS. This possibility cannot be definitively confirmed from our data. Large population studies that compared survival in perinatally acquired HIV with transfusion-acquired disease have shown that differences in HIV mortality between the two groups were due to differences in median symptom-free survival alone. Survival after development of symptoms was similar in the two groups.[23] The possibility that poor nutrition may shorten the symptom-free interval is also suggested by reports on HIV-infected hemophiliacs, in which a decrease in growth velocity identifies children in whom symptoms will develop.[24] The determinants of this nutrition-immunity interaction remain to be delineated.

In summary, perinatally acquired HIV infection is associated with early and progressive growth failure. The severity of growth failure is associated with an increased risk of early mortality. These data suggest that poor nutritional status may play a major role in the progression of asymptomatic HIV infection to AIDS. The effect of early aggressive nutritional intervention in delaying HIV progression and mortality should be evaluated by controlled intervention studies.

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