Mortality in HIV-Infected and Uninfected Children of HIV-Infected and Uninfected Mothers in Rural Uganda

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Objective: To estimate 2-year mortality rates in HIV-1–infected and uninfected infants born to HIV^+ and HIV^- mothers.

Methods: Data are from a prospective study in rural Rakai District, Uganda. Infant HIV status (determined by polymerase chain reaction) was evaluated at 1 to 6 weeks postpartum and during breastfeeding, and maternal HIV viral load and CD4 levels were measured at the postpartum visit. Multivariate Cox proportional hazards models and Kaplan-Meier survival analysis were used to assess survival of infants by maternal and infant HIV status and by quartiles of viral load. Log-rank tests were used to test the equality of survival functions.

Results: Of the 4604 pregnant women, 16.9% were HIV^+, and the proportion of children infected was 20.9%. Median survival of HIV-infected infants was 23 months. Two-year child mortality rates were 128 of 1000 children born to HIV^- mothers, 165.5 of 1000 uninfected children born to HIV^+ mothers, and 540.1 of 1000 HIV-infected children ($P < 0.0001$). Compared with children of HIV^- mothers, the hazard of child mortality was 2.04 ($P < 0.001$) if the mother was $HIV^+$and 3.78 ($P < 0.001$) if the infant was also infected. In the adjusted model, the highest quartiles of $\log_{10}$ HIV viral load in infants and mothers were associated with significantly increased hazard of child mortality (hazard ratio [HR] = 8.54 and HR = 2.50, respectively). Maternal CD4 counts <200 cells/mL were also significant predictors of child mortality (HR = 2.61). A total of 67.6% of HIV-infected children with viral loads above the median died by the age of 2 years and are in need of early antiretroviral therapy (ART).

Conclusions: More than half of HIV-infected infants died at less than 2 years of age. Therefore, ART may need to be initiated earlier in HIV-infected African children.

Key Words: pediatric AIDS, child mortality and HIV, HIV-1 viral load, CD4 count, management of HIV-infected children

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By the end of 2004, it was estimated that more than 2 million children were infected with HIV and that approximately half a million children less than 15 years of age died because of HIV/AIDS, with an additional 640,000 newly infected in that year.[1] A pooled analyses of 9 clinical trials in sub-Saharan Africa found a median survival of 2 years in the absence of treatment; thus, early initiation of antiretroviral treatment (ART) may be desirable.[2] A meta-analysis of US and European studies of untreated or minimally treated children showed more rapid disease progression in children less than 2 years of age and in children with higher viral loads and lower CD4 counts.[3] These findings have assisted in the formulation of treatment initiation guidelines based on clinical staging of disease or CD4 percentage in asymptomatic children.[4,5] In infants, however, CD4 percentage and HIV-1 viral load did not identify rapid progressors in need of early treatment.[6] Mortality among HIV-infected children in developing countries is substantially higher than in the industrialized world,[7,8] and in many settings, CD4 assays are unavailable.

To evaluate the impact of HIV on child survival, it is necessary to assess mortality in HIV-infected and uninfected children born to HIV^+ mothers compared with the background mortality of children born to HIV^- mothers. Although the advent of ART should significantly reduce the morbidity and mortality associated with pediatric AIDS, there are few data to guide decisions regarding treatment initiation in developing country settings. Therefore, we assessed mortality and the predictors of survival in HIV-1–infected children in a rural population in Rakai District, Uganda with a mature generalized HIV epidemic, where 16.2% of pregnant women were infected with HIV.[9]

METHODS

The mothers and children in this study were identified in the Rakai Community Cohort Study (RCCS) between 1994 and 1998.[9,10] The RCCS enrolled consenting adults aged 15

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to 59 years resident in 56 communities and conducted annual surveillance surveys, including censuses, interviews, and collection of samples for HIV and sexually transmitted disease (STD) testing.[9,10]

Pregnant women were identified by interview and by urine human chorionic gonadotropin (HCG) testing at varying durations of gestation (median = 5 months). The children born to these women were assessed after birth, and their survival was monitored by subsequent follow-up surveys. Most mothers and babies were seen within 1 week of birth, when blood samples were obtained for measurement of viral load and CD4 levels. Women and infants were visited at 4 to 6 weeks postpartum and during breast-feeding to assess infant HIV status. The study was reviewed and approved by institutional review boards in Uganda and the United States, and all mothers provided written informed consent for their participation and the participation of their babies. ART and prophylaxis for prevention of mother-to-child transmission (MTCT) were not available at the time of this study.

Women were tested for HIV during pregnancy and postpartum using 2 independent enzyme immunoassays (EIAs; Vironostika HIV-1, Organon Teknika, Charlotte, NC, and Cambridge Biotech, Worcester, MA), with Western blot confirmation of discordant EIA results or seroconverters. Infant HIV infection was detected by reverse transcriptase RNA polymerase chain reaction (RT-PCR) using the Amplicor HIV-1 Monitor 1.5 Assay (Roche Molecular Systems, Branchburg, NJ) on dried blood spots and sera. A serum aliquot was frozen at −70°C and shipped to The Johns Hopkins University (Baltimore, MD) for viral quantification (Amplicor HIV-1 MONITOR Test, version 1.5; Roche Molecular Systems). The lower limit of detection was 400 copies/mL. CD4 lymphocyte count was determined using the TRAx CD4 Test Kit (T Cell Sciences, Needham, MA).[10] PCR results were available from birth to 4 to 6 weeks for 374 infants born to HIV^+ mothers, and in 94 infants, PCR results were available at a subsequent follow-up visit. Children were visited between birth and 4 to 6 weeks to obtain blood samples for PCR. Early HIV infection was defined as a positive HIV test before 6 weeks and late infection by a negative PCR assay at 6 weeks followed by a positive test at a later visit. Among 374 children born to HIV-infected women, 78 (20.9%) were HIV^+ and 296 were uninfected. Among the 78 HIV^+ infants, 69 (88.5%) were followed up. The losses to follow-up were all attributable to maternal out-migration. Of the 296 HIV^- infants born to HIV^+ mothers, 267 children (90.2%) were followed. Of these 267 children, 24 out-migrated and data for 3 children were missing. As a comparison group, we also identified 3404 uninfected children of HIV^- mothers, of whom 3128 (91.9%) were followed up and 276 were lost to follow-up.

Cumulative mortality rates during the first and second years of life were obtained by life table analyses, and the relative risk (RR) of mortality was estimated. Kaplan-Meier survival curves were used to assess the cumulative mortality rates up to 2 years of age, and the adjusted hazard ratio (HR) of child survival was estimated by multivariate Cox proportional hazards models for HIV-infected and uninfected infants born to HIV^+ mothers compared with the referent group of uninfected infants born to HIV^- mothers. Covariates included in the model were those found to be significantly associated with child mortality in the univariate analyses or confounders identified from previous studies. The population attributable fraction (PAF) of child mortality associated with maternal HIV infection was estimated.[11]

Among children born to HIV^+ mothers, we assessed child mortality per 1000 person-years (py) associated with maternal $\log_{10}$ HIV-1 viral load measured at the postpartum visit (categorized into quartiles of <3.53, 3.53–4.25, 4.25–4.66, and >4.66 $\log_{10}$ copies/mL). We also examined the effects of maternal CD4 counts (categorized as <199, 200–499, and ≥500 cells/mL) on infant survival. Among the HIV-infected infants, we assessed the effects on mortality of the infant's $\log_{10}$ HIV-1 viral load, categorized into quartiles (<4.13, 4.13–4.83, 4.83–5.65, and >5.65 $\log_{10}$ copies/mL). CD4 counts were not available for the infants. Maternal socioeconomic status (SES) was controlled for in the multivariate analyses using an additive scale of household possessions and structure (vehicles, radios, household construction materials, electricity, and latrines). A dichotomous measure defined as ≥3 on the additive scale was considered to represent higher SES status, and a measure ≤2 on the scale was considered to represent low SES.

RESULTS

Of the 725 HIV^+ mothers in our sample, HIV PCR tests were available for 374 infants (51.6%). Of these infants, 372 were tested between birth and 6 weeks, and of those negative at 6 weeks, 94 were retested between 6 weeks and 24 months of age to assess breast-feeding HIV transmission. The proportion of children infected during the intrauterine and/or intrapartum period was 16.4% (61 of 372 babies), and

TABLE 1. Estimated Cumulative Mortality Rates At 1 and 2 Years of Age by Maternal and Infant HIV Status Per 1000 Child-Years of Follow-Up

HIV Status	12-Month MR per 1000 (RR)	18-Month MR per 1000 (RR)	24-Month MR per 1000 (RR)
Mother HIV^- Infant HIV^- (N = 3183)	91.0 (1.00)	112.8 (1.00)	128.1 (1.00)
Mother HIV^+ Infant HIV^- (N = 269)	98.7 (1.08)	130.5 (1.16*)	165.5 (1.29)
Mother HIV^+ Infant HIV^+ (N = 69)	309.1 (3.40*)	452.0 (4.0†)	540.6 (4.22†)

*$P < 0.05$.
†$P < 0.001$.
MR indicates mortality rate.

during the breast-feeding period, the rate was 16.0% (61 of 372 babies). The total proportion of children infected with HIV at birth and breast-feeding was 20.9% (78 of 374 babies). Approximately 98% of the women reported breast-feeding, and the median duration of lactation is 20 months in Uganda.[12] There was no information regarding mixed or exclusive breast-feeding.

Table 1 shows cumulative life table mortality rates stratified by infant and maternal HIV status. HIV-infected infants had a significantly higher mortality at all ages compared with HIV^- infants born to HIV^+ mothers ($P < 0.001$) and infants born to HIV^- mothers ($P < 0.001$). The rate ratio (RR) of mortality at 2 years of age in HIV-infected children compared with children born to HIV^- mothers was higher (RR = 4.22; $P < 0.001$). The cumulative mortality rate of uninfected children born to HIV^+ mothers was significantly higher than that of children born to HIV^- mothers at 18 months (RR = 1.16; $P < 0.05$). Kaplan-Meier survival probabilities stratified by maternal and infant HIV status are shown in Figure 1. HIV^+ children had rapid declines in survival starting during the first 6 months of life. The PAF of child mortality associated with maternal HIV infection was 13.8%.

Table 2 shows hazards of child mortality for infants born to HIV-infected women by the mother's HIV viral load and CD4 count. There was an increase in mortality from 49.0 per 1000 py among children of infected mothers whose viral loads were in the lowest quartile up to 217.7 per 1000 py among children of women with viral loads in the highest quartile. The unadjusted HR of child mortality increased with each $\log_{10}$ increase in maternal viral load (HR = 2.02, 95% confidence interval [CI]: 1.5 to 2.7) and with each increase in maternal viral load quartile (χ^2 test for trend = 3.75; $P < 0.001$). Maternal CD4 counts <200 cells/mL were also significantly associated with increased hazard of child mortality. In a multivariate model adjusted for maternal demographic characteristics (SES, age, and education) and

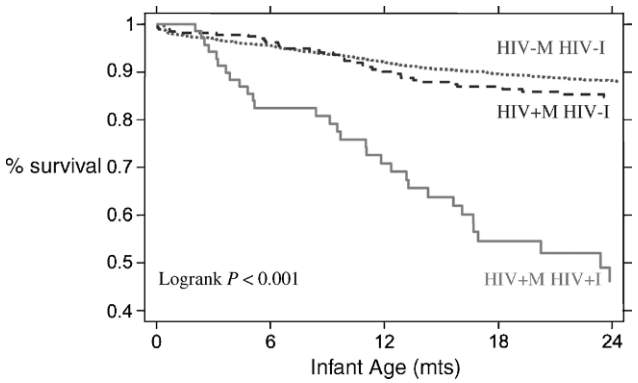

FIGURE 1. Survival of HIV-positive and negative children.

infant low birth weight, the hazard of child mortality was significantly increased in children born to mothers with HIV viral loads between 50th and 75th quartiles (adjusted HR = 3.58, 95% CI: 1.61 to 7.94) and the highest maternal viral load quartile (adjusted HR = 2.50, 95% CI: 1.09 to 0.75). Because of resource constraints, CD4 measurements were available on a smaller sample of women and were not measured in children. Hence, because of overlapping missing information, we were unable to include CD4 levels in the multivariate model.

Table 3 shows child mortality among HIV-infected children by the infant's viral load. Compared with children with viral loads in the lowest quartile, the hazard of mortality was significantly increased in infants with $\log_{10}$ viral loads between 4.83 and 5.65 copies/mL (HR = 5.65, 95% CI: 1.67 to 24.34) and infants with viral loads more than $\log_{10}$ 5.65 copies/mL (HR = 8.54, 95% CI: 2.59 to 33.32, χ^2 test for trend = 3.40; $P < 0.001$).

Kaplan-Meier survival curves for maternal and infant viral loads below and above the median are shown in Figure 2. Mortality in children born to mothers whose

TABLE 2. Mortality by Mother's HIV Viral Load and CD4 Levels

	Deaths/Total N	py	Deaths/1000 py	Unadjusted HR	Adjusted HR
$\log_{10}$ viral load*					
<3.53 (<25%)	10/83	204	49.02	1.00	1.00
3.53–4.15 (25%–50%)	21/76	164	128.05	2.45 (1.11–5.38)	2.17 (0.87–5.39)
4.15–4.66 (50% > 75%)	29/80	149	194.63	3.51 (1.65–7.47)	3.58 (1.61–7.94)
>4.66 (>75%)	27/73	124	217.74	3.57 (1.66–7.65)	2.50 (1.09–5.75)
CD4 count					
>500	24/194	370	64.86	1.00	
200–499	16/101	188	85.11	1.26 (0.65–2.42)	
<199	6/23	30	200.00	2.61 (1.06–6.46)	
SES (ref = low)				1.27 (1.07–1.51)	1.44 (0.81–2.57)
Maternal education (ref = no school)					
Primary school only				0.70 (0.55–0.89)	1.28 (0.4–4.13)
Secondary school plus maternal age (ref age > 30 y)				0.45 (0.31–0.63)	1.1 (0.3–3.93)
15–19 y				1.22 (0.95–1.57)	1.08 (0.41–2.85)
20–30 y				1.07 (0.86–1.34)	1.37 (0.73–2.58)
Low birth weight (ref = low)				1.85 (1.47–2.33)	2.56 (1.42–4.64)

*$P < 0.05$, χ^2 test for trend.
ref indicates reference.

TABLE 3. Child Mortality by Infant's HIV Status and Viral Load (HIV$^+$ Women Only)

	Deaths/ Total N	py	Deaths/ 1000 py	Unadjusted HR
Log_{10} viral load				
<4.13 (<25%)	4/18	37	108.11	1.00
4.13–4.83 (25%–50%)	4/16	28	142.86	1.32 (0.25–7.09)
4.83–5.65 (50%–75%)	11/17	18	611.11	5.65 (1.67–24.34)
>5.65 (>75%)	12/17	13	923.08	8.54 (2.59–36.32)

viral loads were above the median was significantly higher than children of mothers with viral loads below the median (408.3 per 1000 vs. 222.2 per 1000, respectively; RR = 1.84; log-rank χ^2, $P < 0.001$). HIV-infected infants with viral loads above the median had a significantly higher 2-year mortality (826.2 per 1000 infants) compared with infants with viral loads below the median (297.7 per 1000; log-rank χ^2, $P < 0.001$), and 67.6% of HIV-infected children with viral loads above the median died by the age of 2 years.

DISCUSSION

The median survival of HIV-infected children in this rural African population was 23 months, which is compatible with other estimates from sub-Saharan Africa[8] and substantially lower than the median survival observed in Europe and America before the availability of ART.[13–16] The high 2-year mortality in HIV-infected children (540.6 per 1000 children) represents a combination of the direct effects of HIV/AIDS per se and the high background mortality in uninfected children born to HIV$^+$ mothers (165.5 per 1000 children), and we estimate that the excess 2-year mortality attributable to AIDS is 375.1 per 1000 children in this population. In addition, the death rate among uninfected children of HIV$^+$ mothers was higher than among children of HIV$^-$ mothers (128 per 1000 children), suggesting that maternal HIV infection increases risk, even if the children escape infection. Although the mortality rate of HIV$^+$ children in our study is similar to the rates from the pooled trials analyses by Newell et al,[17] the child mortality rate was higher for HIV$^-$ children born to HIV-infected mothers in our study. This may be because the trials were all conducted in urban areas, whereas Rakai is a rural setting. Also, the pooled rates from the trials do not capture the regional variation in child mortality, which was lower in South Africa.[18] A limitation of our study is the loss to follow-up of HIV$^+$ infants, mainly because of out-migration, and the lack of CD4 percentage data or AIDS-defining illnesses in infected children. The analyses only included children who were followed postpartum, however, and the Kaplan-Meier method controls for this type of censoring. A further limitation is that we did not have information on exclusive or mixed breast-feeding.

With the growing availability of ART, clinicians in developing countries face a dilemma in deciding when to initiate ART in infants born to HIV-infected mothers. Assuming that a diagnosis of infant HIV infection can be established, we do not have good predictors of disease progression, and delaying therapy until the onset of symptoms may be too late because of the high risk of mortality, especially in children less than 1 year of age, and because the therapeutic response may be impaired with advanced disease. It has been argued that all infected infants should be treated with time-limited highly active antiretroviral therapy (HAART), because neither CD4 percentage nor viral load could adequately predict children at low risk of disease progression.[18] Newell et al[17] argue for "timely antiretroviral care" rather than universal treatment per se. Our findings support the conclusion of Newell et al,[17] and there is need to reconsider guidelines on the timing of pediatric ART initiation in sub-Saharan Africa, balancing the potential benefits against concerns about adherence, toxicity, and drug resistance.

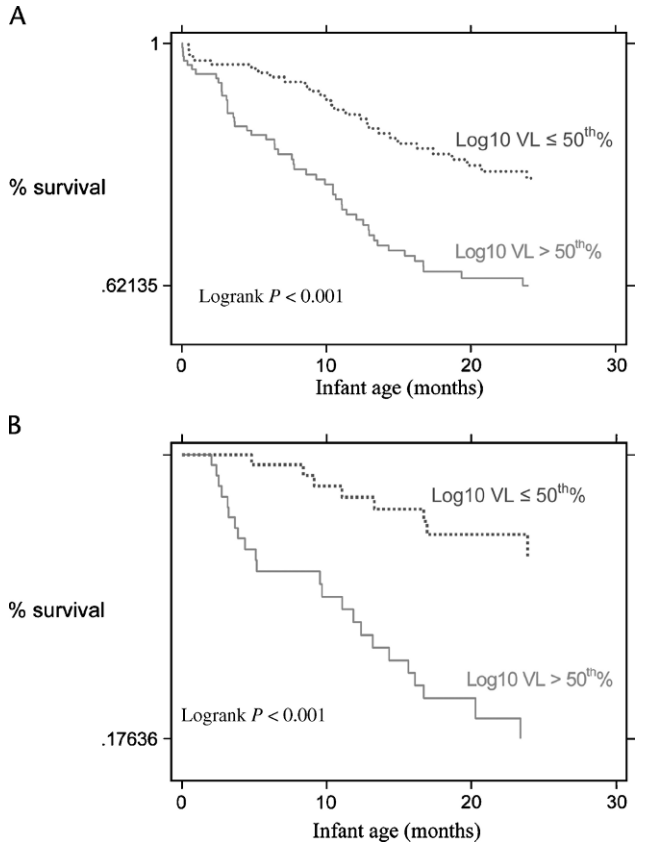

FIGURE 2. Survival of HIV-positive children by maternal (A) and infant (B) median log_{10} viral load levels.

CONCLUSIONS

More than 50% of children infected with HIV died by 24 months of age, and maternal and infant HIV-1 viral loads were predictors of death. These data suggest the need for early initiation of ART.

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