Association of Human Immunodeficiency Virus (HIV) Load Early in Life with Disease Progression among HIV-Infected Infants

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The utility of RNA virus load to predict progression of human immunodeficiency virus (HIV)-1 disease was assessed in 89 HIV-1–infected children. Of 22 virus load values during week 1 of life, 17 were below the detection threshold. Geometric mean virus load increased to $\sim 7 \times 10^5$ copies/mL by week 4, was sustained throughout the first 6 months of life, and then declined to 1.6×10^5 copies/mL during the third year. Samples from week 1 of life had little predictive value, but virus load during days 7–30 strongly predicted progression to CDC-3 classification or death ($P = .024$; risk ratio = 1.6), and virus load during months 2–3 predicted progression to CDC-C or death within the first 6 months of life ($P = .002$, risk ratio = 11). Virus load was highly associated with imminent vulnerability to CDC-C or death ($P = .002$) during the first 18 months of life. Except for values from the first week of life, virus load at any age through 18 months is strongly associated with risk of HIV disease progression.

Human immunodeficiency virus (HIV)-1–infected children manifest variable disease patterns. As many as 20%–30% of perinatally infected children develop an AIDS-defining illness or die by their second birthday; however, the majority of children live significantly longer, sometimes into their second decade [1–4].

Many factors have been proposed to explain the variability of disease manifestations, including timing of transmission [5, 6], maternal health status [7], maternal virus load at delivery [8], gestational age [9], genetic susceptibility [10], and intrinsic characteristics of the virus [11]. For HIV-1–infected adults, a relationship between the HIV-1 RNA virus load and disease progression has been described [12–16]. Similarly, data from a number of studies of infants and children are beginning to delineate the relationship between virus load and disease course in children [17–20].

Several investigators have shown that HIV RNA levels are extremely high during infancy and early childhood compared with levels measured in adults [17–19, 21]. De Rossi et al. [18] described a relationship between the pattern of viral replication early in life and disease outcome in a small cohort of HIV-1–infected children. Similarly, data from a large perinatal cohort, the Women and Infants Transmission Study (WITS) [19], show a strong association between high HIV RNA virus load during early infancy and poor clinical outcome. Mofenson et al. [20] described an independent association of CD4 lymphocyte percentage and RNA level with mortality risk in a cohort of HIV-1–infected children enrolled in an efficacy trial of intravenous immunoglobulin. And Palumbo et al. [17], analyzing data from a large pediatric antiretroviral trial, have shown a strong association between disease progression and baseline RNA levels across a wide range of ages. However, the use of antiretroviral therapy, which may affect virus load or disease progression, was not controlled in these analyses.

To assess the prognostic ability of HIV-1 RNA virus load on disease outcome, independent of antiretroviral use, we present data from a cohort of 86 HIV-1–infected children who were not exposed to zidovudine prophylaxis for the prevention of perinatal transmission; we used only blood samples drawn before initiation of antiretroviral treatment.

Materials and Methods

Study population. Since April 1986, women at risk for HIV infection have been enrolled in a prospective study of perinatal HIV transmission and the natural history of pediatric HIV disease

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Informed consent was obtained from all study participants, according to the guidelines of the US Department of Health and Human Services and those of the institutional review boards of the New York City Department of Health, Medical and Health Research Association, Inc., and the individual study hospitals.

The use of trade names is for identification only and does not imply endorsement by the Public Health Service or the US Department of Health and Human Services.

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progression at eight New York City health care institutions. Protocol design for the larger study has been described elsewhere [22]. Evaluations of pregnant and postpartum women included a detailed questionnaire, periodic physical examinations, disease staging, and phlebotomy. Infants were scheduled for evaluation at delivery, every 2–3 months during the first 18 months of life, and every 6 months thereafter. During each of these visits, a physical examination and phlebotomy were conducted and a medical history was obtained. Hospitalizations, relevant diagnoses, and medications were recorded by study physicians or obtained retrospectively by chart abstraction. Gestational age at birth was determined by the Ballard method.

Determination of infection status and clinical and immunologic categories. Children were classified as HIV-infected and assigned a clinical and immunologic classification according to criteria established by the Centers for Disease Control and Prevention (CDC) in 1994 [23]. In no case was CDC-C classification assigned based solely on the presence of a presumptive AIDS-defining illness. Either AIDS or HIV disease was determined to be a significant underlying factor in all deaths occurring to date in this cohort.

Women were classified as having had AIDS at delivery if they met the criteria of the 1993 Centers for Disease Control revised classification system [24]. Maternal CD4 cell count values used in analyses were those of the last observation in the third trimester of pregnancy or within 2 weeks postpartum.

Laboratory testing. Routine laboratory testing of infant blood samples included a determination of lymphocyte subsets by flow cytometry and of HIV antibody by ELISA and Western blot assay, done at the New York City Department of Health, Bureau of Laboratories. The earliest available infant blood specimens were assayed for the presence of HIV proviral DNA by polymerase chain reaction (PCR) [25].

Blood for virus load studies was collected in standard heparinized vacuum tubes (Becton Dickinson, Rutherford, NJ) and delivered by overnight courier at ambient temperatures to CDC, where peripheral blood mononuclear cells were separated by ficoll-hypaque centrifugation on arrival. Plasma supernatant was aliquoted into radiation-sterilized cryogenic vials (Sarstedt, Newton, NC) and stored at −70°C. Total time from phlebotomy to freezing was 24–30 h. Testing was retrospectively done in batches of these stored samples. Plasma HIV RNA was measured with the nucleic acid sequence–based amplification (NASBA) HIV RNA QT kit (Organon Teknika, Durham, NC), an isothermal nucleic acid amplification assay that has been adapted for use with HIV. The assay was done according to the manufacturer's specifications by personnel blinded to the progression status of the children. The NASBA QT system estimates the amount of RNA in the original sample on the basis of data generated from native RNA and three synthetic internal RNA calibrators. The assay threshold of sensitivity is 1000 RNA copies/mL when 100 μL is used as an input volume of plasma.

Statistical methods. For both biologic and statistical reasons, virus load scores were transformed to base 10 logarithms before analysis. Virus load results below the assay's sensitivity threshold of 10^3 copies/mL were assigned the value of 999. The impact of this technique was investigated by rerunning analyses twice, with subthreshold observations reassigned to the value 500 and to a random number between 1 and 999; no substantial differences were noted between results generated by the three methods.

For analysis, virus load results were grouped by the child's age at phlebotomy as follows: 0–6 days, 7–30 days, 2–3 months, 4–6 months, 7–9 months, 10–12 months, 13–24 months, 25–36 months, and 37–48 months. Children who received postnatal antiretroviral prophylaxis to prevent perinatal transmission were excluded from analysis; virus load results corresponding to samples taken after the initiation of antiretroviral treatment were also excluded. However, in situations in which antiretroviral therapy was introduced after a virus load sample but before an outcome of interest, antiretroviral use was considered as a covariate in the analysis (see below).

Differences between children whose observations were used in the analysis and the remaining infected children in the study were evaluated by Wilcoxon test (continuous variables), Fisher's exact test (categorical variables), or log-rank test (survival to illness or death), as appropriate.

To make maximum use of available data, point estimates and 95% confidence intervals (CIs) of geometric mean virus load by age were derived by use of generalized estimating equations [26]: Virus load measurements to the end of year 3 of life were subjected to a single longitudinal regression analysis, using indicator variables representing the above age groups as predictors of log virus load. An exchangeable within-subject correlation structure was assumed in results reported here, although other structures produced similar results. CIs were constructed from parameter estimates and their respective SEs by use of the usual large-sample method. These values were then exponentiated to yield results in virus load units.

Virus load was then correlated with progression to AIDS (CDC-C classification) or to a surrogate end point, severe immunosuppression (CDC-3). Children who died but did not reach the end point of interest were treated as if they had reached that end point, because all deaths were attributable to HIV and were thus thought to represent an outcome of interest. To assess the association between virus load at any particular age and hazard of imminent progression to these end points, proportional hazards models were constructed that used as a predictor of each outcome all virus load measurements beyond week 1 of life in a time-dependent manner, so that the risk ratio (RR) of log virus load at any particular age was assumed to be a function of the value of log virus load at the immediately preceding measurement. In all such analyses, the occurrence of any antiretroviral treatment between time of virus load measurement and end point (or date last seen) was added as an additional time-dependent dichotomous covariate. It was assumed that once antiretroviral treatment was initiated, it continued without interruption, so that the entire period between antiretroviral onset and the outcome of interest was therefore considered ''treated.'' The addition of age-by–log virus load interaction terms to such models indicated that in most cases the proportional hazards assumption did not hold; for this reason, interaction terms of log virus load with indicator variables representing 6-monthly age groups were used to allow estimation of log virus load RRs separately for different age groups in a single analysis. Overall significance of association of log virus load with outcome was assessed with likelihood ratio tests that compared a model containing these log virus load–by–age group terms plus an antiretroviral treatment term with a model containing only the antiretroviral term. RR estimates are reported here only for 6-monthly age groups having a sufficient number of outcome events to make such estimates

meaningful. To control for other possible confounding variables previously found to be associated with infant disease progression in this cohort [8, 9], additional analyses were done using two additional covariates (gestational age of infant at birth [<37 weeks vs. ⩾37 weeks] and the diagnosis of maternal AIDS before delivery) and only subjects having complete data for all covariates.

To predict these same end points from early virus load results, proportional hazards models were used in a similar fashion; as a predictor, the first log virus load measurement in days 7–30 or months 2–3 of life was used, rather than a time-dependent virus load measure. Antiretroviral treatment and other covariates were used in the same way as before.

Results

Description of Study Population

Of 178 HIV-infected children enrolled into the study between April 1986 and July 1996, 109 had sufficient plasma for at least one virus load result to be obtained. Fifteen of these children were excluded because they and their mothers received prophylactic zidovudine to prevent perinatal transmission or they alone received postnatal zidovudine to prevent perinatal transmission, and 5 others were excluded because their earliest virus load observation was after the onset of antiretroviral therapy. Children born to women who received therapeutic zidovudine during pregnancy were included in the analysis unless the infant also received treatment at birth. The resultant analysis group consisted of 313 virus load observations (1–11/child; median, 3) from 89 children.

Comparison of the 89 children used in the analysis with the study's other HIV-infected children revealed some differences (table 1). Selected children were less likely to be premature, were less likely to test PCR-positive during the first week of life, and had older mothers. Nineteen (21%) of the 89 selected children have died; the median age at death among these 19 was 355 days (range, 29–1404). Median follow-up time among the 70 still-living children was 1100 days (range, 45–3117).

Twenty-seven (30%) of the 89 have progressed to CDC-C classification, with the following earliest AIDS-defining diagnoses: HIV encephalopathy (9), *Pneumocystis carinii* pneumonia (8), recurrent bacterial infections (5), esophageal candidiasis (3), wasting syndrome (1), and disseminated herpes simplex (1). Median age at first CDC-C classification among these children was 271 days (range, 46–1403); 14 of the 27 have died. Five other children have died without reaching class CDC-C; causes of death were sepsis (2), pneumonia (2), and end-stage HIV disease with HIV-associated congestive cardiomyopathy (1).

Forty-three (48%) of the 89 have progressed to CDC-3 classification, at median age 303 days (range, 1–1490). Six other children have died without progressing to that end point.

Sixty-three (71%) of the 89 children received antiretroviral treatment during the course of study, including zidovudine, zalcitabine, didanosine, stavudine, and lamivudine. No children were treated with protease or nonnucleoside reverse transcriptase inhibitors during the observation period.

Table 1. Comparison of characteristics of HIV-infected children included and excluded from analysis.

	Included		Excluded		
Attribute	No. with attribute/ total	%	No. with attribute/ total	%	*P*
Infant male	37/88	42	45/89	51	.293*
Mother African-American	48/85	56	43/86	50	.445*
Maternal AIDS at delivery	2/86	2	8/87	9	.099*
Maternal zidovudine use in pregnancy	16/89	18	21/88	24	.361
Gestational age <37 weeks	24/87	28	38/87	44	.039*
DNA PCR-positive in week 1 of life	7/39	18	15/33	45	.020*
CDC-C or death by 18 months of age	—	33†	—	44†	.117‡
	Median	*n*	Median	*n*	*P*
Mother's age at delivery	28	85	31	85	.004§
Infant birthweight (g)	2731	86	2583	86	.225§
Mother's 3rd trimester CD4 cell count/μL	546	55	476	64	.713§
Infant's earliest CD4 cell count/μL	3082	76	2719	79	.407§

NOTE. PCR, polymerase chain reaction.
* Fisher's exact test.
† Estimated from Kaplan-Meier analysis.
‡ Log-rank test of complete survival.
§ Wilcoxon test.

RNA Virus Load Characteristics

Characteristics of the 313 virus load observations are listed in table 2. Nine of the 89 infants had blood samples available within 48 h of birth. Only 1 of these infants tested PCR-positive during that time; virus load at this observation was 1.5×10^5 copies/mL. One infant who tested PCR-negative had detectable virus load (3.2×10^5 copies/mL) in the corresponding plasma sample from the same blood draw.

Twenty-two (25%) of 89 infants had virus load measurements during the first week of life. Seventeen (77%) of these were below the NASBA detection threshold of 10^3 copies/mL. The other 5 values ranged from 1.5×10^5 to 1.7×10^6. Only 13 (4%) of the remaining 291 samples obtained beyond the first week of life were subthreshold, and all but 4 of these occurred within the first 3 months. Geometric mean virus load increased to a high level of 7.9×10^5 by the end of the first month of life and remained above 6.0×10^5 until months 7–9, then declined somewhat to 2.1×10^5 during months 12–24 (figure 1). The maximum value among the 5 virus load samples obtained between months 36 and 48 was 2.4×10^5.

Table 2. HIV RNA virus load determinations for 313 plasma samples among 89 HIV-infected children during first 4 years of life.

Age interval	Geometric mean virus load (copies/mL)	No. of samples	No. below detection*	No. of children represented	Minimum (copies/mL)	Maximum (copies/mL)
Day 0–6	4.6×10^3	22	17	22	$<1.0 \times 10^3$	1.7×10^6
Day 7–30	5.4×10^5	36	4	33	$<1.0 \times 10^3$	2.8×10^7
Month 2	7.9×10^5	34	2	32	$<1.0 \times 10^3$	3.0×10^7
Month 3	6.9×10^5	31	3	29	$<1.0 \times 10^3$	1.0×10^7
Months 4–6	6.8×10^5	64	0	56	2.3×10^4	1.0×10^7
Months 7–9	5.7×10^5	33	0	29	6.5×10^4	1.4×10^7
Months 10–12	2.8×10^5	30	2	26	$<1.0 \times 10^3$	8.4×10^6
Months 12–24	2.1×10^5	46	2	22	$<1.0 \times 10^3$	3.6×10^6
Months 24–36	1.6×10^5	12	0	9	7.7×10^3	2.1×10^7
Months 36–48	—†	5	0	3	6.1×10^3	2.4×10^5

NOTE. HIV RNA virus load was measured by nucleic acid sequence–based amplification system on 313 plasma samples obtained before antiretroviral treatment in 89 HIV-infected infants who did not receive perinatal zidovudine prophylaxis.

* Threshold of detection for HIV RNA, 10^3 copies/mL.

† Estimate for year 4 observations omitted because of small sample size.

Virus Load and Disease Progression

We sought to determine the correlation of plasma virus load measured in two ways—during the earliest stages of infection (birth to 3 months) and throughout the observation period—with disease progression.

Predictive ability of virus load measured from birth to 3 months of life. Most virus load results in days 0–6 of life were subthreshold and had no ability to predict disease progression. Eight (47%) of the 17 children with undetected RNA in the first week of life progressed to CDC-C classification or death; only 1 of 5 children with detectable RNA (virus load, 4.2×10^5 copies/mL) progressed to CDC-C classification or death (at 162 days of age), while the other 4 had not reached this end point when last seen (at 290, 833, 889, and 1188 days of age) (log-rank test, $P = .414$).

Controlling for use of antiretroviral therapy after virus load measurement and using the earliest virus load determination during days 7–30 of life, we found no significant ability of virus load to predict progression to CDC-C classification or death. However, we found that virus load was predictive in this early period of subsequent progression to CDC-3 classification or death ($P = .042$, $n = 31$). The RR for a 1-log increase in virus load was estimated at 1.6 (95% CI, 1.0–2.6); after controlling for prematurity and maternal AIDS covariates, RR was 1.4 (95% CI, 0.8–2.5; $n = 26$).

Controlling for antiretroviral use after virus load measurement, the earliest virus load determination within months 2–3 (median age, 55 days) was a highly significant predictor of progression to CDC-C classification or death during the period of observation. In this analysis, however, an overall risk estimate could not be determined because the RR was not constant with age. Separate RRs corresponding to 6-monthly age intervals were therefore estimated simultaneously; insufficient data prevented meaningful estimates beyond 18 months of life. The prognostic value of month 2 and 3 virus load scores apparently diminishes with increasing age of the child. The association of virus load in this window with progression to CDC-3 classification or death did not reach statistical significance (table 3).

Association between virus load and immediate hazard of progression. Throughout infancy, vulnerability to both HIV disease end points was strongly associated with the most recent prior virus load measurement, even after adjusting for maternal AIDS and gestational age. RRs were estimated separately for different age ranges (table 4). Again, the strength of association appears to diminish as the child grows older. Kaplan-Meier and linear regression techniques were used to show that the children who had information on both covariates did not differ significantly from the ones who did not, in terms of time to progression to CDC-C classification or death or to CDC-3 classification or death, or in earliest log virus load score controlling for age.

Discussion

In this study of perinatally HIV-1–infected children unexposed to peripartum zidovudine prophylaxis who were followed from birth, we found that RNA virus load attained a very high level within the first few weeks of life, was sustained at these high levels throughout the third year, and was highly associated with disease progression.

The virus load levels described here are 1–2 logs greater than reported in adults during seroconversion or the early latent period after primary infection [12–16]. The high levels reached by 2 months of age among the children reported here were

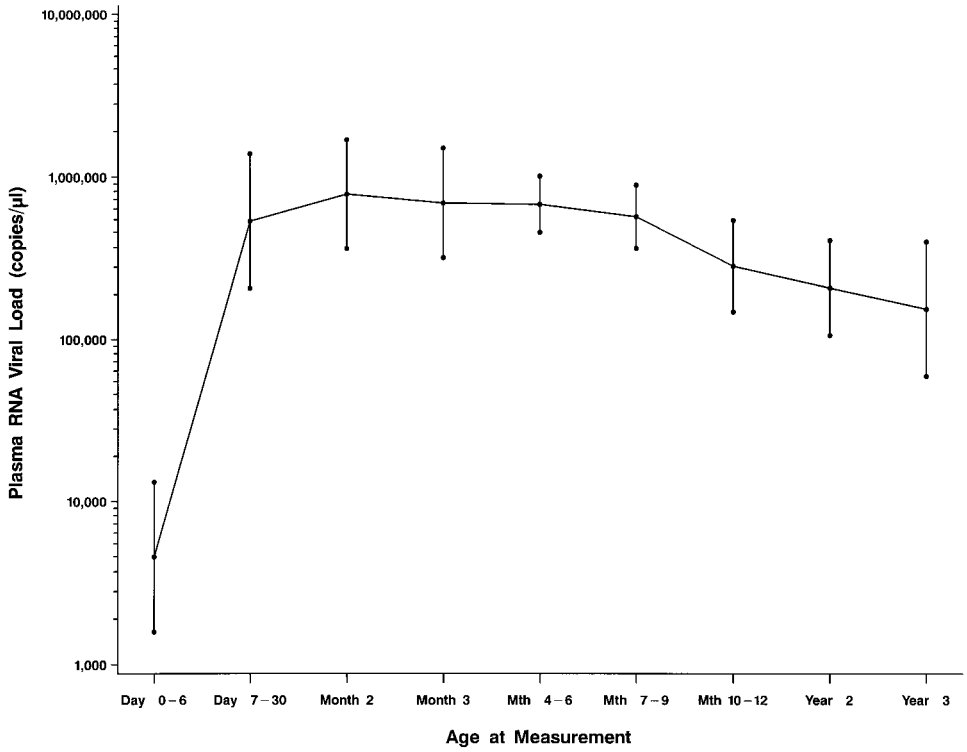

Figure 1. Geometric mean HIV-1 RNA in plasma, associated with 308 observations of 89 HIV-1–infected children by age, with 95% confidence intervals.

nearly 4-fold greater than the peak reported within the first month after seroconversion in adults [27, 28]. Furthermore, virus load stabilized at $\sim 7 \times 10^5$ copies/mL at 2 months in the infants and remained fairly constant for the subsequent 9–12 months. This is in comparison to adults immediately after seroconversion, in whom HIV RNA levels rapidly fall by ~1 log within 30 days of the peak value and continue to decline during the subsequent months. The burst of viral replication in adults following primary infection is believed to be the result of unopposed viral replication in the setting of a naive immune response. The reasons for the high and sustained levels of viral RNA in perinatally infected infants remain to be determined but may be a combination of the immaturity of the infant immune system, increased numbers of available target CD4 cells [29] during the first months of life within which virus production occurs, and/or the potential rapid replenishment of target cells in the developing infant.

The gradual decrease in high virus load levels during late infancy and early childhood shown here and by others may be a result of attrition due to early death of infants with rapidly progressive disease, who are most likely to have highest virus load [17–20, 30]. However, we did see a similar decrease in virus loads during the same period among the children who did not develop rapidly progressive disease (data not shown), suggesting that there is delayed control of viral replication. This may account for the poor survival of infants with perinatally acquired HIV infection compared with infection acquired in adulthood [31]. Samples taken while children were receiving antiretroviral treatment were excluded from the determination of geometric means, and we believe that the values presented in figure 1 provide an accurate depiction of HIV-1 RNA production in this untreated cohort of infants and children.

Perhaps the most important determinant of the sustained high viral replication during early vertical infection is the presence of high levels of target CD4 cells [29, 32]. At birth, absolute CD4 cell counts are high, and their decline over time approximately parallels the decline in virus load during the first several years of life. A predator-prey model between virus and target CD4 cells has been proposed to explain viral dynamics in adults [33] and may apply to infants as well. In this model, the level of viral replication (predator) is determined by the amount of target CD4-bearing cells in which HIV can replicate (prey). This model would explain viral dynamics in early adult infection but would not explain the substantial rise seen in virus load at the terminal stages of disease when circulating CD4 cells are markedly diminished. This model would also explain the sustained high levels of viremia in HIV-infected infants and their subsequent slow decline.

Our finding that virus load as early as the first month of life predicts HIV progression suggests that the disease outcome is determined early in the course of HIV infection. Data from a small cohort studied by De Rossi et al. [18] support this finding. These authors describe three distinct patterns of viral replication during the first weeks of life, one of which indicated that infants who had an early, rapid, and large increase in virus load that was sustained through 2–3 months of age had a

Table 3. Prediction of CDC-C classification or death or CDC-3 classification or death from $\log_{10}$ virus load measured in months 2–3.

	Unadjusted		Adjusted for maternal AIDS, gestational age	
Outcome, age interval	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
CDC-C or death				
Months 1–6	11 (1.2–96)	.002	15 (0.6–403)	.014
Months 7–12	4.9 (0.9–28)	(n = 51)	5.4 (0.6–52)	(n = 36)
Months 13–18	4.7 (0.5–46)		4.5 (0.4–49)	
CDC-3 or death				
Months 1–6	2.1 (0.6–7.2)	.223	3.9 (0.7–22)	.119
Months 7–12	2.6 (0.8–8.5)	(n = 52)	4.2 (0.8–23)	(n = 37)
Months 13–18	1.7 (0.2–12)		1.9 (0.2–17)	

NOTE. Risk ratios are estimates. CI, confidence interval.

poor clinical outcome compared with those who had significant decline after the initial burst of viral replication. Similarly, studies in adults show that the extent of decline after the initial burst of replication during the period of seroconversion is correlated with the rate of disease progression [12, 16].

Data from the WITS cohort [19] show that infants with high virus loads during the first months of life are at increased risk for progression. In addition to supporting the results of the WITS analysis, our data show that virus load during months 2–3 of life is also highly predictive of progression to CDC-C classification or death. A 1-log increase in virus load during this interval resulted in an 11 times greater risk of disease progression or death by 6 months of life. Furthermore, virus load during days 7–30 was found to be predictive of progression to CDC-3 category or death: A 1-log increase resulted in a modest 1.6 times greater risk of immunologic deterioration and death. Our results also complement the findings of Mofensen et al. [20], who reported on the association between HIV-1 RNA levels, CD4 lymphocyte percentage, and mortality among older HIV-1–infected children enrolled in an intravenous immunoglobulin prophylaxis trial. In this study, both baseline RNA level and CD4 lymphocyte percentage at entry were predictive of mortality risk. Children participating in the treatment study were generally older (mean, 3.4 years) than those we studied. Our data, along with those of the WITS and intravenous immunoglobulin studies, indicate that virus load in infants and children, as in adults, is strongly associated with disease progression.

We also found a 3- to 4-fold increase in the risk of clinical and immunologic progression associated with each 1-log increase in most recent virus load measurement any time during the first 12 months of life. These data demonstrate a direct and continuous relationship between HIV-1 RNA levels and the risk of progression in young children. Similar to findings in adults, virus load obtained throughout infancy appears to be both predictive of disease progression and highly associated

Table 4. Association of CDC-C classification or death or CDC-3 classification or death with most recently measured $\log_{10}$ virus load.

	Unadjusted		Adjusted for maternal AIDS, gestational age	
Outcome, age interval	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
CDC-C or death				
Months 1–6	4.4 (1.2–16)	.002	4.4 (1.2–17)	.034
Months 7–12	3.1 (1.1–9.0)	(n = 82)	2.5 (0.8–8.5)	(n = 62)
Months 13–18	3.8 (0.8–18)		1.7 (0.4–7.8)	
CDC-3 or death				
Months 1–6	3.6 (1.4–9.1)	.005	4.3 (1.4–13)	.015
Months 7–12	3.6 (1.4–9.5)	(n = 83)	2.8 (0.8–9.4)	(n = 62)
Months 13–18	1.8 (0.4–8.5)		1.7 (0.3–9.1)	

NOTE. Risk ratios are estimates. CI, confidence interval.

with poor outcome at the time of or immediately subsequent to measurement.

The majority of virus load values obtained in the 22 children during the first week of life were below the level of detection for this assay. While these undetectable values may represent low levels of virus, which could not be measured with our assay, we believe that these findings suggest that perinatal infection in most of these infants occurred during the intrapartum period. Furthermore, our data show that this period of undetectable virus load is short and is followed by a significant and sustained production of virus. This brief period during the first days and weeks of life before viral replication is firmly established may provide a unique opportunity during which infection may be aborted or its extent significantly diminished, either of which has important implications for disease progression. Aggressive antiretroviral therapy within 90 days of birth in a pair of perinatally infected twins has recently been shown to suppress viral replication sufficiently to prevent HIV-specific antibody production in the infant [34]. Similarly, Markowitz et al. [35] have reported preliminary results on 24 adults who began receiving aggressive antiretroviral therapy within 90 days of acquiring infection. After 6–12 months of therapy, a sustained control of viral replication was seen, with RNA levels below the threshold of detection (100 copies/mL), as well as increased CD4 cell counts. Further clinical studies will be needed to determine if the high virus load that rapidly develops in HIV-infected infants can be effectively treated by initiating early, aggressive antiretroviral therapy, as suggested by these limited observations.

Infants were selected for this analysis on the basis of availability of samples. All infants who received antiretroviral medication for perinatal prophylaxis or treatment before sampling were excluded because we believe that HIV RNA levels might be altered by these therapies. The excluded children were significantly more likely to be born prematurely, to test PCR-positive during the first week of life, and to have older mothers. While both prematurity and early detection of virus have been associated with more rapid progression of disease [6, 9], no significant differences in the rate of progression to CDC-C category or death were noted between the 2 groups. Nonetheless, the exclusion of a portion of children with these risk factors for disease progression would likely have underestimated the observed effect of high virus load on disease progression.

Virus load levels reported here may be up to 50% [36, 37] lower than actual circulating levels because of the 24- to 36-h delay in processing samples in this study. However, because the rate of degradation of viral RNA should not systematically differ between children with rapid and nonrapid disease progression, we believe that this delay has not adversely affected our findings. It is notable that the virus load levels reported here were high and similar to levels reported in other studies, including those using other virus load assays [17–20, 30]. Also, different assays for measuring viral RNA levels used in different laboratories and studies should generally not be compared. Therefore, we cannot recommend that the absolute values presented in this study be used in the clinical setting.

Our data suggest that the pattern of disease for HIV-1–infected children may be determined during the first weeks of life. We are hopeful that the initiation of aggressive antiretroviral therapy during this crucial time period will effectively reduce virus burden and significantly alter the natural history of this disease in children. Out data suggest that aggressive antiretroviral therapy of infants and young children may improve their clinical course.

Study Group Members

Other members of the New York City Perinatal HIV Transmission Collaborative Study include the following. New York City Department of Health: Sarah T. Beatrice, Mary Ann Chiasson, Erica DeBernardo, William Oleszko, Amado Punsalang; Medical and Health Research Association of New York City, Inc.: Tina Alford, Abraham Betre, Mark Cappelli, Nancy Cruz, Julia Floyd, Virginia Foye-Sousou, Lynn Jackson, Dorothy Jones Jessop, Luis Macias, Debbie Ng, Katherine Nelson, Roxanne Savory, Hany Tadros, Sadarryle Young; Harlem Hospital Center: Aretha Belmore, Susan Champion, Julia Floyd, Cynthia Freedland, Susan Lovich, Pamela Prince, Adrienne Rogers, Maria Suarez; Metropolitan Hospital Center: Roger Henriquez, Pratibha Ankola, Hamida Khakoo, Sarla Inamdar, Elmer Agustin, Lynn Jackson, Nancy Cruz, Eileen Sacharzky; Bronx Lebanon Hospital: Marilyn Crane, Patricia Campbell, Joanna Dobrosycki, Ivan Hand, Ziv Harish, Adell Harris, Laurie Soloman, Aileen Steiner, Andrew Wiznia; Montefiore: Marcella Naccarato, Graveola Brooks, Marjorie Nicholson, Marquerite Mayers, Mayris Webber; Centers for Disease Control and Prevention: Sherry Orloff and RJ Simonds.

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