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Decline of CD3-positive T-cell counts by 6 months of age is associated with rapid disease progression in HIV-1–infected infants

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Abstract

Because HIV-1 infected infants with rapid progression (RP) of disease might benefit from early and intense antiretroviral therapy, the identification of predictive factors of RP becomes extremely important. Currently, the best predictive factors of RP in HIV-1 infected children are HIV-1 RNA levels and CD4-positive T-cell counts. A decrease in CD3-positive T-cell count has been identified as a predictive factor of AIDS development in HIV-1 infected adults. Our objective was to evaluate decreased number of CD3-positive T-cells as a predictive factor of RP in infants. Peripheral blood lymphocytes from HIV-1 infected infants (up to 6 months of age) were analyzed for an association of lymphocyte subsets with RP, which was defined as the occurrence of AIDS or death before 18 months of age. In infants with RP ($n = 32$), CD3-positive T-cell counts were 3093 cells/ μ L at <1 month of age, 3092 cells/ μ L at 1 to 3 months, and 2062 cells/ μ L at 3 to 6 months. Non-RP infants ($n = 49$) maintained their CD3-positive T-cells counts at approximately 4000 cells/ μ L for at least 6 months of life. CD3-positive and CD4-positive T-cell counts were significantly associated with RP. Our results suggest that a decreased CD3-positive T-cell count may be used to predict RP in HIV-1 infected infants ($RR = 2.16$, $P = .001$).

Keywords

HIV-1; AIDS; rapid disease progression; infants; CD3-positive T-cell counts

Vertical transmission of HIV-1 still occurs at significant levels in medically underserved inner-city communities and underdeveloped countries.¹ More than 20% of HIV-1 infected infants develop Centers for Disease Control and Prevention (CDC) class C disease² (equivalent to AIDS) or die before 18 months of age.³ Early antiretroviral therapy for HIV-1 infected infants has been recommended, particularly those with rapid progression (RP) of disease.⁴ Several studies have suggested different surrogate markers to assess the risk of RP

in pediatric populations, including HIV-1 RNA levels, lymphocyte subsets, and serum proteins.^{5,6} Increasing HIV-1 RNA levels are good predictors of disease progression in infants and children, though there is a large overlap of the HIV-1 RNA plasma values of HIV-1 infected infants who develop AIDS early with those of HIV-1-infected infants who stay asymptomatic.⁷ A low CD4-positive T-cell count is also a strong determinant of HIV-1 disease progression.⁵

In HIV-1 infected adults, decreases in CD3-positive T-cell counts occur 1.5 to 2.5 years before the development of AIDS, independently of CD4-positive T-cell counts.⁸ Therefore, we hypothesize that the analysis of CD3-positive T-cells in HIV-1-infected infants could be used to assess the risk of RP in a large cohort of subjects, such as the Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P²C²) Study (1990–1996).⁹

METHODS

Study population

The P²C² Study population has been described earlier, and explanations of recruitment, examinations, laboratory analysis, and quality assessment have been presented.⁹ For this longitudinal study, we analyzed children who were born to HIV-1-positive women and prospectively enrolled at birth or by 28 days of life (birth cohort). Ninety-three of 600 infants enrolled were infected with HIV-1; they were examined at intervals of 3 to 6 months through 5 years of age. Progression to CDC class C disease or death was considered rapid if it occurred before 18 months of age. The relatively high incidence of RP (43.5%) in our cohort has been discussed previously.⁹

T-cell determination

CD3-positive, CD4-positive, and CD8-positive T-cell numbers were determined by means of 2- or 3-color fluorescence flow cytometry in laboratories certified by the National Institute of Allergy and Infectious Diseases, AIDS Quality Assurance Program. Absolute numbers were determined arithmetically on the basis of complete blood counts from the same blood sample and expressed as numbers of cells per microliter of blood.

Statistics

CDC stage-specific cumulative morbidity and mortality were estimated through use of the Kaplan-Meier method. Repeated measures analyses of lymphocytes (cube-root transformations) were performed by means of SAS Proc Mixed (Cary, NC), which estimated the means and 95% CIs according to disease progression and age. To estimate the relative risk (RR) of RP and to examine the temporal relationship between lymphocyte phenotypes and RP, we included each of the phenotype measures as a time-dependent covariate in a Cox regression model of disease progression. The Cox model was fit separately for each T-cell subset.

RESULTS

Morbidity and mortality of HIV-1 infected infants

Table I summarizes the cumulative morbidity and mortality according to the CDC classification system. By 18 months of age, 10.9% of the children had died and 32.6% were in class C (AIDS). Forty HIV-1-infected infants (43.5%) had reached class C or died by 18 months of age. Over 90% of the infants took antiretroviral medications. Most of the infants were African American (44.1%) or Hispanic (34.4%).

Lymphocyte subset analysis

T-cell subset counts available after 1 week and up to 6 months of age and before the identification of CDC class C symptoms were used in the lymphocyte subset analyses. Among the 93 HIV-1-infected infants, 81 had data (128 measurements) available for analysis, 8 did not have data before 6 months of age, and 4 had CDC class C symptoms before the earliest T-cell measurement. The mean CD3-positive T-cell counts were lower in HIV-1-infected infants who were subsequently identified with RP ($n = 32$) than in non-RP HIV-1-infected infants ($n = 49$). Mean CD3-positive T-cells were significantly lower before 1 month of age ($P = .05$), at 1 to 3 months ($P = .05$), and at 3 to 6 months ($P < .001$) in the infants with RP (Fig 1). Mean CD3-positive T-cell counts were approximately 4000 cells/ μ L at each age category in the non-RP subgroup but declined from 3093 cells/ μ L before 1 month and 3092 cells/ μ L at 1 to 3 months of age to 2062 cells/ μ L at 3 to 6 months in the RP subgroup. The mean CD3-positive T-cell count remained lower in HIV-infected infants with RP after adjustment for maternal CD3-positive T-cell count and zidovudine exposure in utero.

A total of 36 infants received antiretroviral therapy. There was no significant effect on CD3-positive T-cell counts associated with receiving antiretroviral therapy ($P = .24$). Mean CD4-positive T-cell counts ($P = .002$ and $P < .001$ at 1 to 3 months and 3 to 6 months, respectively) and mean CD8-positive T-cell counts ($P < .001$ at 3 to 6 months) were lower in RP infants than in non-RP infants. CD8-positive T-cell counts initially increased in all of the infants but decreased sharply at 3 to 6 months of age in those with RP. In non-RP infants, the CD8-positive T-cell counts remained stable (Fig 1). The estimates of RR of developing RP of HIV-1 disease were elevated on the basis of CD3-positive T-cells (RR = 2.16 per 2000 cells/ μ L decrease; 95% CI, 1.36–3.40; $P = .001$) and CD4-positive T-cells (RR = 2.30 per 1000 cells/ μ L decrease; 95% CI, 1.52–3.47; $P < .001$) but not on the basis of CD8-positive T-cells (RR = 1.44 per 1,000 cells/ μ L decrease; 95% CI, 0.91–2.27; $P = .12$). The 5-year cumulative survival was lower for children with baseline CD3-positive T-cell counts below the median (49.7%; SE, 8.1) than for children with baseline counts above the median (85.5%; SE, 5.5; $P < .001$). The association between CD3-positive T-cell count and survival remains significant ($P < .006$) after adjustment for serum IgG levels, albumin levels, and HIV-1 RNA load.

DISCUSSION

The progression of HIV-1 infection to AIDS is thought to occur when the immune system is unable to control viral replication and there is subsequent destruction of CD4-positive T-cells. CD8-positive T-cells are major components of the antiretroviral immune response. In subjects with RP, CD8-positive T-cell counts initially increased when CD4-positive T-cell counts decreased, but they subsequently fell. The presence of anti-HIV-1-specific CD8-positive T-cells correlates with long-term survival¹⁰; however, the value of CD8-positive T-cell counts for prognosis of HIV-1 disease progression is controversial. The rise and following decline of CD8-positive T-cell numbers might be responsible for the lack of statistically significant association with progression of disease. In the present study, the total T-cell population, assessed by the measurement of CD3-positive T-cell counts, is predictive of RP in HIV-1 infected infants. Using the same patient cohort, we have previously shown that a high baseline CD4-positive T-cell count and a low baseline HIV-1 viral load were significant independent factors associated with survival, in agreement with similar studies in the literature.⁶

The use of the total number of T cells as an indicator of HIV-1 disease progression is based on the concept of blind T-cell homeostasis.⁸ This theory proposes a regulatory mechanism that keeps the total number of T cells constant, increasing the number of CD8-positive T cells when the number of CD4-positive T cells decreases. When both CD8-positive and CD4-positive T-cell counts drop, the development of AIDS occurs. Evidence showing that the decreased number of CD3-positive T cells is an indicator of AIDS progression in children has not been reported. The determination of CD3-positive T-cell counts might provide additional information needed to make the decision to start early antiretroviral treatment in HIV-1 infected infants and therefore delay the disease progression.

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Abbreviations used

RP	Rapid progression
RR	Relative risk
CDC	Centers for Disease Control and Prevention
P²C²	Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection [Study]
CD4-positive T-cells	Helper T-cell subpopulation
CD8-positive T-cells	Cytotoxic T-cell subpopulation

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Appendix

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A complete list of the study participants can be found elsewhere.⁹

FIG. 1.

T-cell subset counts from HIV-infected infants with RP of disease (○) and HIV-infected infants with non-RP of disease (●) during their first 6 months of age. **A**, CD3-positive T cells. **B**, CD4-positive T cells. **C**, CD8-positive T cells. The numbers of subjects at each time interval are given under the graphs.

TABLE I

Cumulative morbidity and mortality for HIV-1-infected children

Age	A/B/C/death*				B/C/death				C/death				Death				Percent at each CDC clinical category [†]			
	N _R	N _E	%	SE	N _R	N _E	%	SE	N _R	N _E	%	SE	N _R	N _E	%	SE	A	B	C	D
3	59	34	36.6	5.0	75	18	19.4	4.1	86	7	7.5	2.7	92	0	0	—	17.2	11.9	7.5	0
6	37	56	60.2	5.1	54	39	41.9	5.1	73	20	21.5	4.3	90	2	2.2	1.5	18.3	20.4	19.3	2.2
12	16	75	81.3	4.1	37	54	58.4	5.1	57	34	36.8	5.0	84	8	8.7	2.9	22.9	21.6	28.1	8.7
18	9	82	89.5	3.3	29	62	67.4	4.9	51	40	43.5	5.2	82	10	10.9	3.3	22.1	23.9	32.6	10.9
60	3	83	91.2	3.2	8	73	83.2	4.4	11	50	58.6	5.9	24	28	32.7	5.2	8.0	24.6	25.9	32.7

N_R: Number of children who are still being followed at that age without the event; *N_E*: number of children who are still being followed at that age who have had the event; %, estimated percent who have had the event.

* Clinical stage of HIV-1 disease (class A, B, or C indicative of mild, moderate, or severe symptoms), according to the 1994 CDC pediatric classification system.