

EARLY PROGRESSION OF DISEASE IN HIV-INFECTED INFANTS WITH THYMUS DYSFUNCTION

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ABSTRACT

Background Infants with congenital thymic deficiency (the DiGeorge syndrome) have immunodeficiency and a characteristic pattern of low CD4+ and CD8+ T-lymphocyte counts and low CD5+ B-lymphocyte counts. Because the thymus is essential for the generation of CD4+ cells, we sought evidence of thymus dysfunction in infants infected perinatally with the human immunodeficiency virus (HIV).

Methods We studied the immunophenotypes of 59 infants with maternally transmitted HIV, 5 infants with the DiGeorge syndrome, and 168 infants exposed to HIV but not infected. The criteria for a presumed thymic defect were reductions in both the CD4+ and CD8+ T-cell subgroups during the first six months of life that were confirmed in a subgroup of infants by low counts of CD4+CD45RA+ and CD4+CD45RO+ T cells and CD5+ B cells.

Results Of the 59 HIV-infected infants, 17 had immunophenotypes similar to those of infants with the DiGeorge syndrome. The risks of the acquired immunodeficiency syndrome (AIDS) by the ages of 12 and 24 months were, respectively, 75 percent and 92 percent in these 17 infants, as compared with 14 and 34 percent in the other 42 infants ($P < 0.001$). Nine of the HIV-infected infants with the DiGeorge-like immunophenotype (53 percent) died within six months of the progression to AIDS, as compared with only three of the other infants (7 percent, $P = 0.006$).

Conclusions In some infants infected perinatally with HIV, a pattern of lymphocyte depletion develops that resembles the pattern in congenital thymic deficiency. Since HIV disease progresses rapidly in such infants, they may be candidates for early antiviral therapy and attempts at immune reconstitution. (N Engl J Med 1996;335:1431-6.)

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PERINATAL human immunodeficiency virus (HIV) infection generally has a more rapid course than HIV infection in adults.^{1,2} The pattern of progression is bimodal, with the acquired immunodeficiency syndrome (AIDS) developing in a subgroup of infants very early in life and progressing much more slowly in others.³⁻⁶ These distinct patterns imply differences in pathogenesis. The hallmark of disease progression is the depletion of CD4+ T cells, which has generally been attributed to HIV-induced destruction of lymphocytes by various mechanisms.² However, defective generation of CD4+ cells by the thymus, caused by

HIV, could also contribute to such depletion, particularly in young children in whom the thymus is more active.⁷ HIV-infected children have low counts of CD4+CD45RA+ cells,⁸ which are believed to originate in the thymus.⁷ Several other reports have suggested thymic involvement in HIV infection. These include histopathological examinations of the thymus of HIV-infected fetuses and children⁹⁻¹² and virologic studies in patients,^{13,14} thymic cultures,¹⁵⁻¹⁷ and SCID-hu mice.¹⁸⁻²⁰

Infants with severe congenital thymic anomalies (the DiGeorge syndrome) have immunophenotypic profiles characterized by low counts, not only of CD4+ and CD8+ T cells, but also of CD5+ B cells (unpublished data). We have also found low CD5+ B-cell counts in some HIV-infected infants less than one year old.²¹ To examine further a possible relation between the congenital and acquired immune defects, we studied immunophenotypes and assessed thymic involvement in infants with maternally acquired HIV infection and infants exposed to HIV but not infected with it. We also examined the relation of the immunophenotypes associated with a "thymic defect" to the progression of HIV disease.

METHODS

Study Population

We selected 59 children with perinatal HIV infection and a control group of 168 HIV-exposed but uninfected infants, born after 1985, in whom immunophenotypic studies had been performed at least once during the first six months of life. Forty of the infected infants were identified by prenatal screening of their mothers and were followed prospectively from birth, and the other 19 were referred to our center before the age of six months either because the mother was known to be seropositive for HIV (8 infants) or because the infant had an illness compatible with a diagnosis of HIV infection (11 infants). Five infants with severe cases of the DiGeorge syndrome (two boys and three girls; mean age at the start of the study, 3.1 months) were included for comparison. The diagnosis of the DiGeorge syndrome was made on the basis of previously described criteria.^{22,23}

Follow-up data on the HIV-infected and the HIV-exposed infants were collected at regular intervals in our pediatric clinics. The diagnosis of HIV infection was based on the criteria of the Centers for Disease Control and Prevention (CDC) for pediatric HIV infection,²⁴ with an age of 18 months used as the cutoff age for persistently positive serologic tests. Seropositive infants below that age

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TABLE 1. ABSOLUTE LYMPHOCYTE COUNTS DURING THE FIRST SIX MONTHS OF LIFE IN HIV-INFECTED PATIENTS WITH THE THYMIC-DEFECT PROFILE, HIV-INFECTED PATIENTS WITHOUT THE PROFILE, AND CONTROLS EXPOSED TO, BUT NOT INFECTED WITH, HIV.

LYMPHOCYTE SUBGROUP	HIV-INFECTED PATIENTS		CONTROLS (N = 168)
	THYMIC DEFECT PRESENT* (N = 17)	THYMIC DEFECT ABSENT (N = 42)	
	median no. of cells/mm ³ (10th–90th percentiles)		
T cells			
CD3+	937 (171–1432)	3494 (2400–5720)	4252 (2741–6379)
CD8+	512 (158–813)	1214 (729–2450)	1191 (640–2457)
CD4+	536 (26–1088)	2139 (1336–3280)†	314 (1990–4650)
CD45RA+‡	467 (51–2688)	2428 (880–3093)	2872 (1131–4709)
CD45RO+‡	138 (46–1309)	546 (87–1309)	718 (201–1182)
B cells			
CD5+§	126 (17–493)	1594 (642–2036)	1075 (430–2086)

*P<0.05 for the comparisons with HIV-infected patients without the thymic-defect profile and with controls for each lymphocyte subgroup shown.

†P<0.05 for the comparison with the control group.

‡Data are based on the study of 7 patients with the thymic-defect profile, 9 patients without the profile, and 54 controls.

§Data are based on the study of 10 patients with the thymic-defect profile, 9 patients without the profile, and 42 controls.

were considered to be infected with HIV if they had at least two positive tests for HIV by the polymerase chain reaction, the immune-complex-dissociated p24 antigen assay, or both, or if they had an AIDS-defining condition. The clinical status of infected children was determined according to the criteria of the CDC.

Flow Cytometry

A whole-blood staining technique was used to quantitate subpopulations of mononuclear cells in peripheral blood by direct two-color immunofluorescence, as previously described.⁸ Specific cell-surface markers were identified by the following pairs of monoclonal antibodies (Becton Dickinson) conjugated with fluorescein isothiocyanate (FITC) or phycoerythrin (PE): Leucogate (CD45 and CD14); Simulstest isotype control FITC–IgG1 and PE–IgG2a; Simulstest FITC–CD3 and PE–CD4; FITC–CD3 and PE–CD8; FITC–CD5 and PE–CD19; FITC–CD4 and RD1–2H4 (for CD45RA+); and FITC–CD4 and RD1–4B4 (for CD45RO+). Because the last three of these markers were introduced in 1992, subgroups of CD5+ B cells, CD4+CD45RA+ (naive) T cells, and CD4+CD45RO+ (memory) T cells were studied in only about one third of the infants. A single-laser flow cytometer (FACScan, Becton Dickinson) that distinguishes between forward and right-angle scatter of light was used with an appropriate software package (Simulset, Becton Dickinson).

Immunospot Assays

Enzyme-linked immunospot (Elispot) and reverse enzyme-linked immunospot (Relispot) assays, described previously by our group,^{25,26} were used to quantitate the cells secreting specific antibodies to HIV glycoprotein 160 (gp160) and the total number of cells secreting IgG, respectively.

Statistical Analysis

Because patients with the DiGeorge syndrome have both low CD4+ counts and low CD8+ counts, these counts were studied jointly in the noninfected controls (when more than one lymphocyte-subgroup measurement was made in the first six months of

life, the later value was used). Infants in whom both of these counts were below the 5th percentile of the joint distribution in the control group during the first six months of life were defined as having the thymic-defect immunotype. This approach was validated in the infants whose CD5+ B-cell counts we studied.

Lymphocyte subgroups were quantitated in the HIV-infected and the HIV-exposed (but uninfected) control populations at intervals of approximately three months and were characterized with standard descriptive statistics, including medians and ranges (from the 10th to the 90th percentile). Kruskal–Wallis tests and Wilcoxon rank-sum statistics were used to compare the distributions of lymphocyte counts in the study groups. Characteristics of the progression of disease were compared by the chi-square test or Fisher's exact test. Data on the time to an event were described with Kaplan–Meier estimates, and the corresponding comparisons between groups were made with generalized Wilcoxon test statistics. All P values are two-sided and unadjusted for multiple comparisons.

RESULTS

HIV-Infected Patients

AIDS developed during the first year of life in 19 of the 59 HIV-infected children studied (10 boys and 9 girls). In the remaining 40 infants (21 boys and 19 girls), either AIDS developed after the first year of life (17 infants) or it had not developed by the time of the last follow-up after the age of one year (23 infants). AIDS was diagnosed at a median age of 4.0 months among the infants in whom it developed during the first year and (by Kaplan–Meier estimate) at an age of 40.5 months among the other infants. When the infants referred to the center were included in the analysis, the proportion of infants with AIDS in the first year of life was overestimated (19 of 59, or 32 percent); among the HIV-infected

infants followed prospectively from birth, this proportion was 16.6 percent.

Studies of Lymphocyte Subgroups

In the control group, the 5th percentile of the values measured during the first six months of life was 1900 per cubic millimeter in the case of CD4+ cells and 850 per cubic millimeter in the case of CD8+ cells. Infants in whom both the CD4+ and CD8+ counts were below these values were considered likely to have a thymic defect. Seventeen such infants were identified (the "thymic defect" group); they were compared with the remaining 42 HIV-infected infants (the "no thymic defect" group). The differentiation between the groups was validated on the basis of the markedly low CD5+ B-lymphocyte counts noted among 10 infants in the thymic-defect group whose CD5+ B-cell counts were obtained, as compared with the counts in 9 infants tested in the no-thymic-defect group and 42 infants in the control group (Table 1).

The proportion of all HIV-infected children studied who had the thymic-defect profile was thus 29 percent (17 of 59). However, among HIV-infected infants followed prospectively from birth, the proportion was 15 percent (6 of 40).

Table 1 shows the median CD3+, CD4+, and CD8+ T-lymphocyte counts in the groups with and without the thymic-defect profile and in the HIV-exposed but uninfected controls. Although the CD4+ counts were significantly lower in the no-thymic-defect group than in the controls, the distributions of CD8+ counts in these two groups were similar. The absolute CD4+CD45RA+ and CD4+CD45RO+ counts were lower in the infants with the thymic-defect profile than in the infants without that profile or the controls (Table 1). The percentage of CD4+CD45RA+ cells was slightly lower in the thymic-defect group (83 percent) than in either the no-thymic-defect group (88 percent, $P=0.04$) or the controls (89 percent, $P=0.02$) (data not shown). The percentage of CD4+CD45RO+ cells did not differ significantly among the three groups (thymic-defect group, 23 percent; no-thymic-defect group, 20 percent; controls, 20 percent).

When we studied only the 10 patients with the thymic-defect profile whose CD5+ B-cell counts had been obtained, we found that their CD3+ counts (median, 1300 per cubic millimeter), CD4+ counts (median, 640 per cubic millimeter), and CD8+ counts (median, 475 per cubic millimeter) were similar to those in the thymic-defect group as a whole.

Changes in the counts of CD4+ and CD8+ T cells during the first year of life in the two groups of HIV-infected infants and the controls are shown in Figure 1, along with corresponding values in the infants with the DiGeorge syndrome. The differences be-

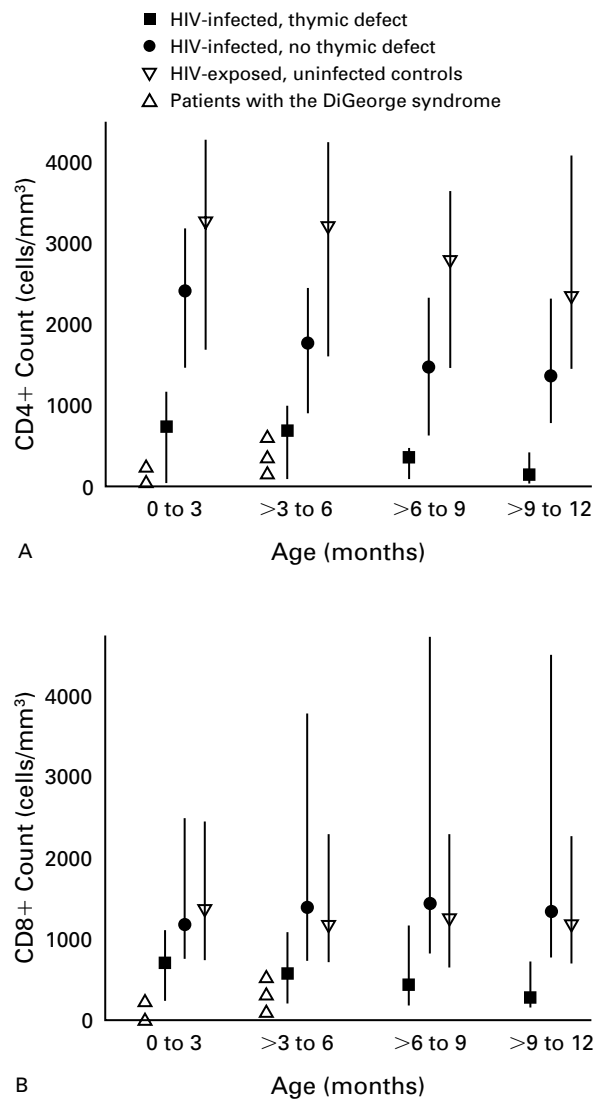


Figure 1. T-Lymphocyte Counts during the First Year of Life in HIV-Infected Patients with and without the Thymic-Defect Profile and Controls.

Medians and ranges (from the 10th to the 90th percentile) of the CD4+ count (Panel A) and the CD8+ count (Panel B) are shown for three-month intervals, with corresponding values for patients with the DiGeorge syndrome.

tween the groups in CD4+ cell counts during the first six months of life were maintained during the second six months. The median CD4+ counts in the thymic-defect group were significantly lower than those in the no-thymic-defect group and were close to the values in patients with the DiGeorge syndrome. The similarity between the patients in the thymic-defect group and the patients with the DiGeorge syndrome was also evident with regard to CD8+ cell counts. In contrast, the CD8+ counts in the patients without the thymic-defect profile rose

above those of the uninfected controls after the first three months and remained slightly higher thereafter.

Correlation of Immunophenotypes with the Progression to AIDS

Among the 17 infants with the thymic-defect profile, AIDS developed in 14 during the first year of life, in 1 at 13 months, and in 1 at 20 months; the remaining infant did not yet have AIDS at the age of 36 months. In comparison, AIDS developed during the first year of life in 5 of the 42 infants in the no-thymic-defect group, and the remaining 37 infants in that group had a slower progression to AIDS or no such progression. Figure 2 shows Kaplan–Meier plots of the risk of AIDS and of survival

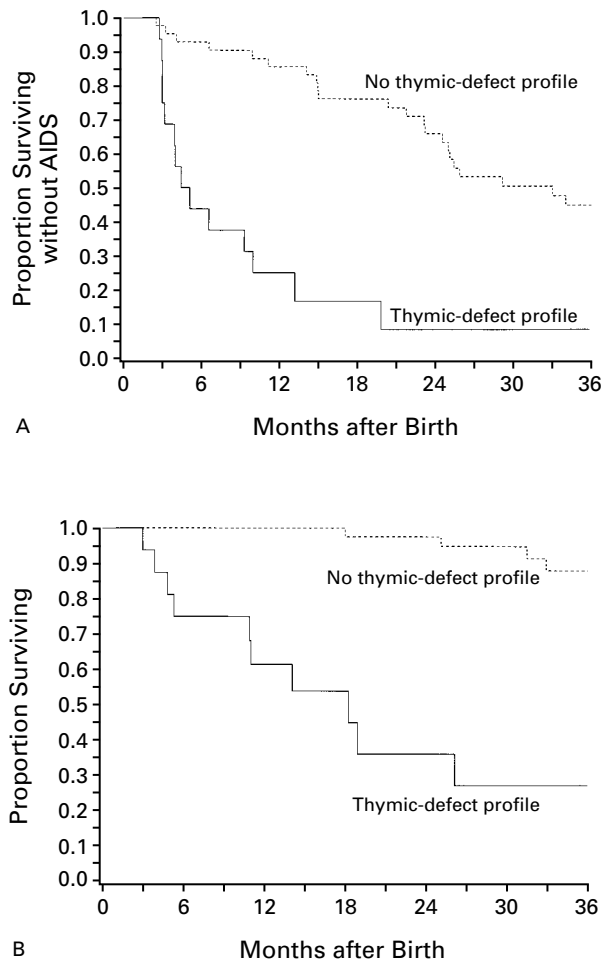


Figure 2. Kaplan–Meier Plots of Clinical Outcomes in HIV-Infected Infants in the First Three Years of Life, According to Whether the Thymic-Defect Profile Was Present in the First Six Months.

Panel A shows the proportion of infants in whom AIDS developed, and Panel B shows the proportion who survived. $P < 0.001$ by the generalized Wilcoxon test for the comparison between groups in both analyses.

for the two HIV-infected groups. The risk of the development of AIDS was 75 percent within 12 months and 92 percent within 24 months in the thymic-defect group, as compared with 14 percent and 34 percent, respectively, in the no-thymic-defect group ($P < 0.001$) (Fig. 2A). The risk of dying of AIDS was 38 percent within 12 months and 64 percent within 24 months in the thymic-defect group, as compared with 0 and 3 percent, respectively, in the group without the thymic-defect profile ($P < 0.001$) (Fig. 2B). The difference in survival is not entirely due to the fact that the AIDS diagnoses occurred earlier in the thymic-defect group. Even after the AIDS diagnosis, there was a difference in survival between the two groups; 9 of 17 infants in the thymic-defect group (53 percent) died within six months after their AIDS diagnosis, as compared with only 3 of 42 infants in the no-thymic-defect group (7 percent, $P = 0.006$) (data not shown).

We further analyzed the specific clinical findings in the HIV-infected infants. *Pneumocystis carinii* pneumonia occurred more frequently in the thymic-defect group (8 of 17, or 47 percent) than in the no-thymic-defect group (6 of 42, or 14 percent; $P = 0.015$) and was the principal cause of AIDS and death in the patients with the thymic-defect profile. The median survival after the diagnosis of *P. carinii* pneumonia was one month for the patients in the thymic-defect group. Among the six patients in the no-thymic-defect group in whom *P. carinii* pneumonia developed, two died, 8 and 27 months after diagnosis; the other four remained alive 24 to 49 months after the diagnosis.

Among the 5 infants of the 42 in the no-thymic-defect group in whom AIDS was diagnosed during the first year of life, the diagnosis was due to *P. carinii* pneumonia in 4 and to encephalopathy and esophageal candidiasis in 1. Only one of these five patients died, at the age of 31 months; the other four were still alive after the age of 2 years. These five infants had slower and less marked decreases in the CD4+ count, and higher CD8+ counts, than the infants with the thymic-defect profile.

Other opportunistic infections, recurrent bacterial infections, and encephalopathy were more common than *P. carinii* pneumonia among the infants in the no-thymic-defect group. However, these conditions did not differ significantly in frequency between the two groups, which probably reflects the fact that the infants in the thymic-defect group died at earlier ages. Hypogammaglobulinemia early in life, as evidenced by low serum immunoglobulin levels, low counts of immunoglobulin-secreting cells as detected by the Relispot assay,²⁶ or both, was noted in 3 of 8 infants with thymic-defect profiles but none of 28 infants without this profile who were tested ($P = 0.007$). The measurement of cells secreting specific antibodies against gp160 with the Elispot assay²⁵ showed that

by six months of age none of 8 patients tested in the thymic-defect group had B cells that secreted such antibodies, as compared with 17 of 21 tested in the no-thymic-defect group ($P < 0.001$).

DISCUSSION

The acquired immunodeficiency associated with HIV is characterized by a depletion of CD4+ T cells that results from the direct or indirect effects of the virus.² In adults and many pediatric patients, CD8+ T-lymphocyte counts are often elevated until the end stage of AIDS, possibly because of "blind homeostasis"²⁷ (the theory that as the CD4+ counts decrease in HIV infection the CD8+ counts increase so that the total number of CD3+ T cells remains constant). In contrast, the severe congenital immunodeficiency due to thymic aplasia is associated with marked decreases in both CD4+ and CD8+ lymphocytes, since both T-cell subgroups require a functional thymus in order to develop. We have recently detected decreases in CD5+ B cells in infants with the DiGeorge syndrome (unpublished data). Such cells (or B-1a cells) normally constitute more than 60 percent of the total number of B cells in the first year of life, decreasing to adult levels (10 to 30 percent) by the age of three years.²¹ These cells make up a substantial proportion of the small number of B lymphocytes found in the thymus of mice²⁸ and humans²⁹; in the latter, they have been postulated to play a part in the negative selection of autoreactive T-cell clones.³⁰

In this study, we have identified a subpopulation of HIV-infected infants with an immunophenotype resembling that of patients with the DiGeorge syndrome. Our findings suggest that the pathogenesis of disease in this group of infants may involve HIV-induced dysfunction of the thymus. The prominent role of the thymus in the development of T-cell immunity in the fetus and young child^{7,31} makes it reasonable to assume that damage to this organ induced by HIV would have far greater consequences in young children. Thymic lesions were seen in the fetuses of HIV-seropositive mothers who underwent either spontaneous¹¹ or intentional¹² abortion. Almost all the HIV-infected infants we studied who had the thymic-defect profile had a rapid progression to AIDS during their first year and subsequently survived a significantly shorter time than HIV-infected children without this profile. We postulate that in children with such a defect, early disruption of the thymic microenvironment by HIV results in a reduced post-thymic reservoir of lymphocytes in peripheral lymphoid sites. The heavy demand for CD4+ cells to regenerate in order to compensate for the HIV-induced post-thymic destruction² would be expected to exhaust this smaller reservoir rapidly and cause early progression of disease. Thus, the bimodal pattern of progression in pediatric AIDS³⁻⁶

may be explained largely by differences in the potential of HIV strains to cause early thymic disruption.

There have been variable histopathological findings on examination of the thymus in specimens obtained at autopsy from patients who died of AIDS at various ages⁹⁻¹² and in macaques infected with simian immunodeficiency virus who have severe immunodeficiency.³² These findings include combinations of thymitis, disruption of the stromal architecture, loss of Hassall's corpuscles, and thymocyte depletion. These features were all observed at autopsy in the thymus of one of our patients with the thymic-defect profile, who died at the age of nine months.

Strains of HIV differ in their effects on thymic epithelium and thymopoiesis in culture¹⁵⁻¹⁷ and in SCID-hu mice.¹⁸⁻²⁰ Particularly relevant is a recent observation indicating that viral strains from one child with rapid progression of HIV disease and another with slow progression have different effects on thymopoiesis in culture.¹⁷ In a young adult with HIV infection, thymus-derived viral clones had more affinity for thymocytes than did viral clones in peripheral blood,¹⁴ and their genotypic and phenotypic characteristics differed.

Other investigators have noted an increased risk of rapid disease progression in infants with virus detected soon after birth, lower CD4+ counts at an early age, and higher degrees of viral replication as measured by the quantitative polymerase chain reaction or the p24 antigen assay.^{6,33,34} We do not yet have sufficient data on the early detection of virus or on the viral load in enough infants with and without the thymic-defect profile. However, the very early depletion of T lymphocytes in the affected infants in the thymic-defect group reinforces the likelihood that the virus was transmitted in utero. If this is indeed the case, it may be expected that the proportion of infants found to have the thymic-defect profile will be larger among HIV-infected infants whose mothers received zidovudine³⁵ late in gestation or only at delivery than among those whose mothers received zidovudine earlier.

The proportion of infants with the thymic-defect profile was 15 percent among the HIV-infected infants we followed prospectively, but a larger sample is required for this proportion to be assessed more accurately. All our patients with the thymic-defect profile continued to have marked lymphopenia after the first six months of life, except for one patient, who had a slight and transient increase in the CD8+ count to about 1100 cells per cubic millimeter.

In addition to their pathogenetic importance, our findings have clinical implications that include the need for prompt identification of patients in whom AIDS progresses early and who have the thymic-defect profile. The recent recommendations for early prophylaxis against *P. carinii* pneumonia in all HIV-

exposed children³⁶ may prove particularly beneficial in children under the age of six months, and thereafter if HIV infection is demonstrated. Therapeutic approaches will need to be more aggressive among these infants, with earlier use of antiviral agents and perhaps even immune reconstitution with thymic transplantation.³⁷

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CORRECTION

Early Progression of Disease in HIV-Infected Infants with Thymus Dysfunction

Early Progression of Disease in HIV-Infected Infants with Thymus Dysfunction . On page 1432, in the last column of Table 1, the median number of CD4+ lymphocytes in the controls should have been 3142, not 314, as printed. We regret the error.