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CYTOMEGALOVIRUS INFECTION AND HIV-1 DISEASE PROGRESSION IN INFANTS BORN TO HIV-1–INFECTED WOMEN

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Abstract

Background and Methods—Cytomegalovirus (CMV) has been implicated as a cofactor in the progression of human immunodeficiency virus type 1 (HIV-1) disease. We assessed 440 infants (75 of whom were HIV-1–infected and 365 of whom were not) whose CMV status was known, who were born to HIV-1–infected women, and who were followed prospectively. HIV-1 disease progression was defined as the presence of class C symptoms (according to the criteria of the Centers for Disease Control and Prevention [CDC]) or CD4 counts of less than 750 cells per cubic millimeter by 1 year of age and less than 500 cells per cubic millimeter by 18 months of age.

Results—At birth the frequency of CMV infection was similar in the HIV-1–infected and HIV-1–uninfected infants (4.3 percent and 4.5 percent, respectively), but the HIV-1–infected infants had a higher rate of CMV infection at six months of age (39.9 percent vs. 15.3 percent, P=0.001) and continued to have a higher rate of CMV infection through four years of age (P=0.04). By 18 months of age, the infants with both infections had higher rates of HIV-1 disease progression (70.0 percent vs. 30.4 percent, P=0.001), CDC class C symptoms or death (52.5

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percent vs. 21.7 percent, P=0.008), and impaired brain growth or progressive motor deficits (35.6 percent vs. 8.7 percent, P=0.005) than infants infected only with HIV-1. In a Cox regression analysis, CMV infection was associated with an increased risk of HIV-1 disease progression (relative risk, 2.59; 95 percent confidence interval, 1.13 to 5.95). Among children infected with HIV-1 alone, but not among those infected with both viruses, children with rapid progression of HIV-1 disease had higher mean levels of HIV-1 RNA than those with slower or no progression of disease.

Conclusions—HIV-1–infected infants who acquire CMV infection in the first 18 months of life have a significantly higher rate of disease progression and central nervous system disease than those infected with HIV-1 alone.

Although numerous epidemiologic, pathological, and in vitro molecular studies have implicated cytomegalovirus (CMV) as a cofactor in the pathogenesis of the acquired immunodeficiency syndrome (AIDS), a direct causal relation has been difficult to document, since most adult patients are infected with CMV long before becoming infected with human immunodeficiency virus type 1 (HIV-1).[1–15] In contrast, children acquire primary CMV infection either at the same time as or after they acquire HIV-1 infection. Thus, the effect of CMV on the progression of HIV-1 disease can be more easily studied in children. Moreover, because in infants and children both HIV-1 and CMV infections usually occur during important periods of development, there may be major clinical, virologic, and immunologic interactions between the two infections. We examined the association of CMV infection with the progression of HIV-1 disease in a cohort of 600 prospectively enrolled infants.

METHODS

Patient Population

The Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study is a prospective, multicenter study of the natural history of cardiovascular and pulmonary disorders and associated risk factors in children with vertically transmitted HIV-1 infection. Patient recruitment and the study population have been previously described.[16] The study was initiated after institutional review board approval at each center, and patients were enrolled after written informed consent was obtained.

Among 600 infants born to HIV-1–infected women, 432 (72.0 percent) were enrolled while their mothers were pregnant and 168 (28.0 percent) before 28 days post partum. Among 93 HIV-1–infected infants, 29 (31.2 percent) were enrolled postnatally (median, 12 days; range, 1 to 28). HIV-1 infection was diagnosed if a child had two positive HIV-1 cultures, had a positive HIV-1 antibody test at 15 or more months of age, died of an HIV-1–associated condition, or had AIDS. Infants with two negative HIV-1 cultures (one at 5 or more months of age) or negative HIV serologic results at 15 or more months of age were considered to be HIV-1–uninfected. All others were considered to be of indeterminate status with respect to HIV-1.

Children through five years of age underwent serial immunologic evaluation by standard flow-cytometric techniques and serum HIV-1 RNA quantitation by the Amplicor HIV-1 Monitor Test (Roche Diagnostic Systems, Branchburg, N.J.) with a lower limit of detection

of 400 HIV-1 RNA copies per milliliter.[17] The 1994 revised classification system of the Centers for Disease Control and Prevention (CDC) was used to classify infants according to the immunologic and clinical stage of HIV-1 disease (category 1, 2, or 3, or class A, B, or C).[18] HIV-1 disease progression was defined as the presence of CDC class C symptoms (AIDS-defining conditions) or CD4 counts of less than 750 cells per cubic millimeter (CDC category 3) before 1 year of age and less than 500 cells per cubic millimeter by 18 months of age.

CMV Studies

Local centers performed all CMV urine cultures with standard virologic techniques (shell-vial or standard culture) and CMV IgG and IgM antibody testing with commercially available enzyme immunoassays during pregnancy for women, and at birth and every six months thereafter for infants. The CMV cultures and serologic tests were monitored by an external interlaboratory quality-assurance program with a respective sensitivity and specificity of 100 percent and 98 percent for CMV cultures, 95.4 percent and 94.7 percent for IgG assays, and 90.0 percent and 86.8 percent for IgM assays. Among the infants who were HIV-1–positive, those who were CMV-negative had a median of six CMV cultures and five serologic tests, and those who were CMV-positive had a median of five CMV cultures and three serologic tests. Cultures of saliva were performed in a subgroup of infants.

The CMV polymerase chain reaction (PCR) was performed on frozen urine samples collected at one institution. Samples from only two children produced repeatedly positive results, which were confirmed later by culture and serologic testing.[19] A child who had a positive culture of urine or saliva or a positive result on PCR of urine at any age, or who had a positive serologic test for IgG or IgM at 12 or more months of age, was considered CMV-infected. Only one HIV-1–positive child had a positive CMV IgM test at two years of age. Serologic results for 13 children receiving intravenous immune globulin were excluded.

Patients more than six months of age were considered CMV-uninfected if they had a negative serologic test and no positive culture results on or before the date of the negative serologic test. An infant with a positive CMV culture in the first 21 days of life was considered to have been infected in utero.[20]

Statistical Analysis

Cumulative rates of CMV infection among children who were free of congenital CMV infection were obtained from a Weibull model[21] in which the dependent variable was the time to CMV infection (interval-censored), fitted separately for the HIV-1–infected and HIV-1–uninfected groups. The cumulative percentage with CMV infection at age *t* was then estimated as $\hat{\theta}+(1-\hat{\theta})\,\hat{F}(t)$, where $\hat{\theta}$ is the estimated percentage congenitally infected and $\hat{F}(t)$ is the estimated percentage infected by age *t* from the Weibull model.

The relation between disease progression and CMV infection was examined by comparing Kaplan–Meier estimates of progression in those infected and not infected with CMV at 6, 12, and 18 months of age. The generalized Wilcoxon test was used to compare overall

incidence. When the Kaplan–Meier estimates match the simple fractions of patients with disease progression because of the lack of censoring, we report the numerators and denominators of the simple fractions as well. To examine the temporal relation between CMV infection and disease, we included CMV infection as a time-dependent covariate (yes or no) in a Cox regression model of time to disease progression or death. The multiple-imputation method was used to impute times of CMV infection on the basis of a Weibull model, conditional on disease status at 18 months and on the left and right censoring times defining the intervals containing the times of CMV infection. The results from 300 multiply imputed data sets were combined to estimate the relative risk of disease progression.[22,23] These Cox regression analyses focused on disease events only in the first 18 months of life.

Longitudinal analyses of lymphocyte subgroups (cube-root transformation of counts) and serum HIV-1 RNA ($\log_{10}$) were performed by SAS Proc Mixed, which provided estimates and 95 percent confidence intervals for the means according to HIV-1 status, CMV status, and age. CMV status was a time-dependent covariate, since at any age the CMV status could change irrevocably from uninfected to infected. Reported P values are two-sided.

RESULTS

CMV Infection According to Age

Among the 600 infants enrolled, 93 were HIV-1–infected (median age at first positive culture, 3.2 months), 463 were HIV-1–uninfected, and 44 were of indeterminate HIV-1 status; 51.5 percent were black, 30.3 percent were Hispanic, and 52.7 percent were male. Figure 1 shows the rate of CMV infection according to age and HIV-1 status, with 75 infected and 365 uninfected infants having known CMV status. The incidence of in utero CMV infection was similar for HIV-1–infected and HIV-1–uninfected infants: 2 of 47 (4.3 percent) vs. 9 of 200 (4.5 percent). However, HIV-1–infected infants had a higher rate of CMV infection at six months of age (39.9 percent vs. 15.3 percent, P=0.001), and the cumulative rates of CMV infection over time among HIV-1–infected children were significantly higher through four years of age (P=0.04).

Clinical Outcome in HIV-1–Infected Children

We assessed the effect of CMV infection on HIV-1 disease progression in two ways: first, by analyzing the available data on CMV infection at 6, 12, and 18 months in relation to HIV-1 disease progression, and second, by performing a Cox regression as described in the Methods section.

Infants infected with both HIV-1 and CMV at 6, 12, and 18 months were more likely to have disease progression than those infected with HIV-1 alone. At 6 months, 7 of 13 infants with HIV-1 and CMV (53.8 percent) and 5 of 38 with HIV-1 alone (13.2 percent) had disease progression (P=0.006); at 12 months, 15 of 23 with HIV-1 and CMV (65.2 percent) and 7 of 29 with HIV-1 alone (24.1 percent) had disease progression (P=0.001); at 18 months, 28 of 40 with HIV-1 and CMV (70.0 percent) and 7 of 23 with HIV-1 alone (30.4 percent) had disease progression (P=0.001). Kaplan–Meier estimates of disease progression at 18 months

are shown in Figure 2A. These differences continued through 4 years of age (P=0.002 for overall incidence, with the use of CMV status at 18 months).

Infants with both infections were also more likely than those with HIV-1 infection alone to have class C symptoms or to have died by 18 months of age (52.5 percent vs. 21.7 percent, P=0.008 at 18 months and P=0.02 for overall incidence), as shown in the Kaplan–Meier plot in Figure 2A. Class C symptoms in the first 18 months of life are summarized in Table 1. Class C CMV disease was seen in three children, all of whom had other AIDS-defining conditions.

Infants with both infections were more likely than those with HIV-1 infection alone to have HIV-1–associated encephalopathy at 18 months (35.6 percent vs. 8.7 percent, P=0.005), including impaired brain growth (5 of 40 vs. 0 of 23) and progressive motor deficits (11 of 40 vs. 2 of 23), as shown in the Kaplan–Meier plots in Figure 2B. As with disease progression, these measures of HIV-1 disease outcome were significantly associated with CMV status at 6 and 12 months of age as well (data not shown). Data on CMV cultures in the first 21 days of life were available for only 8 of the 14 children who had central nervous system disease by 18 months, but all cultures were negative.

Cox regression analysis indicated that CMV infection during the first 18 months of life raised the risk of HIV-1 disease progression (relative risk, 2.59; 95 percent confidence interval, 1.13 to 5.95; P=0.02). The risk remained elevated after adjustment for maternal CD4 percentage (the percentage of lymphocytes that were CD4-positive) (relative risk, 2.53; P=0.05). The results of the Cox regression analysis also suggested that CMV infection raised the risk of class C symptoms or death (relative risk, 2.46; 95 percent confidence interval, 0.95 to 6.36; P=0.06) and HIV-1–associated encephalopathy (relative risk, 2.90; 95 percent confidence interval, 0.86 to 9.74; P=0.08).

The cumulative 18-month death rate was 5.0 percent for infants infected with both viruses at 18 months (as compared with 0 percent for those with HIV-1 infection alone), and this difference increased with age (27.5 percent vs. 0 percent mortality at 3 years and 30 percent vs. 9.4 percent mortality at 4 years, P=0.06 for overall incidence).

Immunologic Measures and CMV Infection

The effect of CMV infection on the immune system was evaluated, with CMV status modeled as a time-dependent covariate with children classified according to their CMV status at each age tested (Fig. 3). As expected, both CD4 counts and CD4 percentages were lower in HIV-1–infected infants. Children infected with both viruses had significantly lower mean CD4 counts at 15 months of age (Fig. 3A) and lower CD4 percentages at 1, 3, and 15 months of age than those infected with HIV-1 alone (data not shown).* Among HIV-1–uninfected infants, the mean CD4 percentages were also lower for those infected with CMV at the ages of three and nine months. The mean CD8 count was significantly higher in infants infected with both viruses at 1, 9, 30, 42, and 54 months of age (Fig. 3B), and the

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CD8 percentage was higher at 1 month and at all times measured over 9 months of age.* Among HIV-1–uninfected infants, the mean CD8 percentage was significantly higher at most ages for those with CMV, and the mean CD8 count was higher at 3, 9, 15, 21, and 54 months of age.

Serum HIV-1 RNA Levels, CMV Infection, and Progression of HIV-1 Disease

HIV-1 RNA levels were also examined according to age and HIV-1 disease progression by one year of age, with CMV status again modeled as a time-dependent covariate, as for lymphocytes. Mean levels were not significantly different in CMV-infected and CMV-uninfected children. Among CMV-uninfected children, those with rapid progression of HIV-1 disease had higher mean levels of HIV-1 RNA at all ages than those with slower or no progression. Among CMV-infected children, there were no significant differences in HIV-1 RNA levels between those with rapid progression of disease and those with slower progression, except for children 24 months of age (Fig. 4).

Characteristics of the Mothers of CMV-Positive and CMV-Negative Children

The mean maternal age, rate of CMV seropositivity, rate of CMV viruria, rate of pregnancy complications (bleeding or prolonged [>24 hr] rupture of membranes), and the gestational age of the infant were similar in mothers of infants with and without congenital CMV infection. However, in comparison with mothers of CMV-uninfected infants, mothers of infants infected with CMV by six months of age had significantly lower mean CD4 counts (371 vs. 507 cells per cubic millimeter, P=0.003), CD4 percentages (20.8 percent vs. 28.5 percent of lymphocytes, P<0.001), and CD19–CD20 counts (129 vs. 172 cells per cubic millimeter, P=0.04). They also had marginally higher rates of CMV viruria (16.7 percent vs. 5.6 percent, P=0.06) and CMV seropositivity (100 percent vs. 90.5 percent, P=0.09) and lower rates of bleeding or prolonged rupture of membranes (P=0.02). These differences were not observed among mothers of HIV-1–negative infants.

Infants of Unknown CMV Status at 18 Months

Of the 93 HIV-1–infected infants, 30 were of unknown CMV status at 18 months. Six of the 30 children died before CMV studies had been performed, and 5 others were lost to follow-up before 18 months of age. Two children who died had negative CMV results more than six months before death and were classified as having unknown CMV status at the time of death. Finally, eight children had no CMV tests before 18 months, and for nine children the timing of CMV studies was such that their CMV status at 18 months of age could not be determined.

DISCUSSION

This cohort-based, prospective study of CMV infection in the offspring of HIV-1–infected mothers has several notable findings. Although the rate of in utero CMV infection (4.5 percent) was higher than in most non-HIV-1–infected populations, it was not significantly different between HIV-1–infected and HIV-1–uninfected infants. In contrast, perinatal and postnatal CMV infection was strikingly more common among HIV-1–infected infants. Moreover, infants with early CMV infection appeared to have more rapid progression of

HIV-1 disease. More than half of infants with both infections had an AIDS-defining condition or died by 18 months of age. Most of the AIDS-defining conditions in infants with both infections were not due to CMV infection itself, but they did include substantial central nervous system involvement, particularly impaired brain growth and progressive motor deficits. The mechanism by which dual infection with CMV and HIV-1 led to these changes was not clear, but it appeared to be something other than an increase in the plasma HIV-1 RNA level.

Since early in the AIDS epidemic, CMV has been implicated as a cofactor in the progression of HIV-1 disease and the pathogenesis of AIDS.[1–15] Although Webster et al.[14,15] reported that CMV-positive patients were more likely to have CDC class IV disease than CMV-negative patients, it has been difficult to show a simple correlation in adults between CMV infection and rapid progression of HIV-1 disease,[7,11,12,24] largely because CMV infection is virtually universal in HIV-1–infected adults. However, studies of children and more recent quantitative analyses of CMV infection and CMV viremia in both children and adults have shown a correlation between CMV infection and an advanced stage of HIV-1 disease.[6,25–32] Reports of simultaneous infection with HIV-1 and CMV among adult patients in whom rapidly progressive disease developed may, in fact, be analogous to the findings reported here.[33–36]

CMV and HIV-1 can infect the same cells, and the cellular proteins and viral gene products of each virus can activate the other virus in vitro.[2,5,13,37–39] Other possible mechanisms of enhancement of HIV-1 infection by CMV include enhanced expression of Fc receptors, facilitating infection with HIV-1 in complex with immunoglobulin; activation of monocytes and T cells; and up-regulation of genes for cytokines and cellular factors, even in abortively infected cells.[40–42] Since both viruses are immunosuppressive, they may act additively or synergistically to accelerate disease progression.[43,44]

The most striking finding of this study was the frequency of progressive neurologic disease in infants with combined HIV-1 and CMV infection. Although the mechanism of this effect was not elucidated in this study, it is interesting that cytomegalic inclusion disease in otherwise normal infants is characterized by impaired brain growth (microcephaly) and progressive motor deficits, as seen here.[45] It is possible that CMV in dually infected infants causes damage in the same areas as in cytomegalic inclusion disease. HIV-1 and CMV may infect the same cells in the brain and retina.[37,38,46,47] CMV has been detected in brain endothelial cells, macrophages, and astrocytes both in vitro and at autopsy,[46] whereas HIV-1 has been detected primarily in microglia and macrophages. Microglial nodules are found in patients with AIDS and those with CMV central nervous system disease.[48,49]

There was a positive association between mean HIV-1 RNA levels and disease progression in infants who were infected only with HIV-1, but not in infants who were infected with both HIV-1 and CMV. This implies that coinfection accelerates disease progression not by enhancing overall HIV-1 replication, but by other mechanisms, such as increased immunosuppression, combined effects of HIV-1 and CMV on local replication, combined pathologic effects of two independent viral infections, or exaggerated immunopathologic effects or tissue damage due to soluble mediators.

Although the 4.5 percent rate of in utero CMV infection in this cohort was higher than the overall rates of 0.2 to 2.2 percent for the general population, it was similar to that in a recently described Brazilian cohort, but lower than the 21 percent rate recently reported in another U.S. cohort.[50,51] Perhaps as a reflection of the high seroprevalence of CMV in our maternal cohort, no infant had typical cytomegalic inclusion disease. HIV-1–uninfected infants had a cumulative rate of CMV infection of 15.3 percent at six months of age; most of these infections were probably acquired perinatally in these formula-fed infants. In contrast, the rate of CMV infection in the HIV-1–infected group at six months of age was 39.9 percent. This increase in the infection rate could be caused by higher levels of cervical CMV shedding in women who transmitted HIV-1 to their infants at birth. Positive cervical CMV cultures have been shown to be correlated with perinatal CMV infection,[52] but we did not perform cervical CMV cultures. CMV infection rates in the HIV-1–infected group continued to climb rapidly over the next 12 months. It is possible that the mothers who transmitted HIV-1 to their infants had more advanced immunodeficiency and shed more CMV in the saliva or urine than the mothers who did not transmit HIV-1. Alternatively, HIV-1–infected infants may have been more susceptible to horizontal CMV infection.

Our results strongly imply that any attempts to prevent CMV infection in the offspring of HIV-1–infected women will have to target the perinatal period and the first 18 months of life. By six months of age, 13 infants were already coinfected with CMV, and in 8 of them the disease later became rapidly progressive. Early coinfection may also be important in developing countries, where both viruses may be transmitted at the same time in breast milk. Potential preventive strategies include early prophylaxis with anti-CMV drugs, the administration of high doses of hyperimmune CMV antibody, and vaccination.

In conclusion, HIV-1–infected and HIV-1–uninfected infants had similar rates of in utero CMV infection, but HIV-1–infected infants had higher rates of CMV infection acquired perinatally or during the first four years of life. CMV coinfection was significantly correlated with rapid progression of HIV-1 disease and with devastating early central nervous system disease in some HIV-1–infected infants. Strategies for the prevention of CMV infection in these high-risk infants should be the focus of future research.

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APPENDIX

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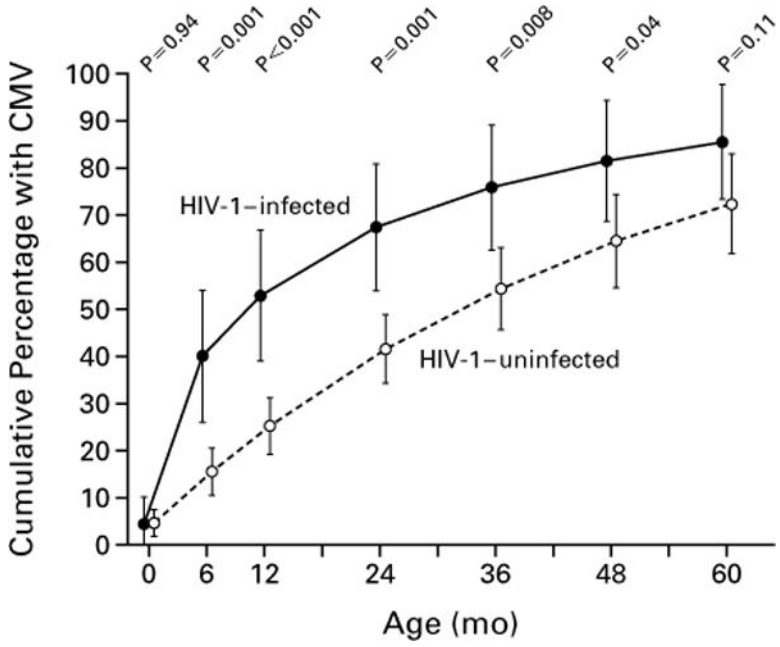

Figure 1.

Estimated Cumulative Rates of CMV Infection over Time among HIV-1–Infected and HIV-1–Uninfected Children.

At the end of follow-up, 52 HIV-1–infected children were confirmed to be CMV-infected, 23 were CMV-uninfected, and 18 were of unknown status. Of the 463 HIV-1–uninfected children, 144 were CMV-infected, 221 were CMV-uninfected, and 98 were of unknown status. I-bars indicate 95 percent confidence intervals.

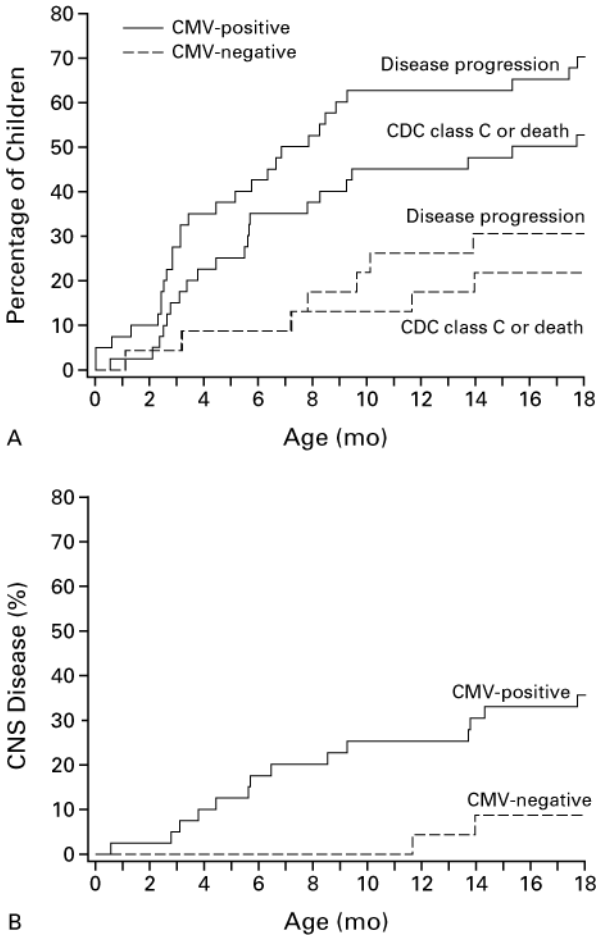

Figure 2.

Cumulative Rates of Morbidity and Mortality Due to AIDS in HIV-1–Infected Children According to CMV Status at 18 Months of Age.

Forty children had CMV infection, and 23 did not. Thirty additional children had unknown CMV status. Panel A shows the cumulative incidence of disease progression (P=0.001) and of CDC class C symptoms or death (P=0.008). Panel B shows the cumulative incidence of central nervous system (CNS) disease (impaired brain growth or progressive symmetric motor deficits) (P=0.005).

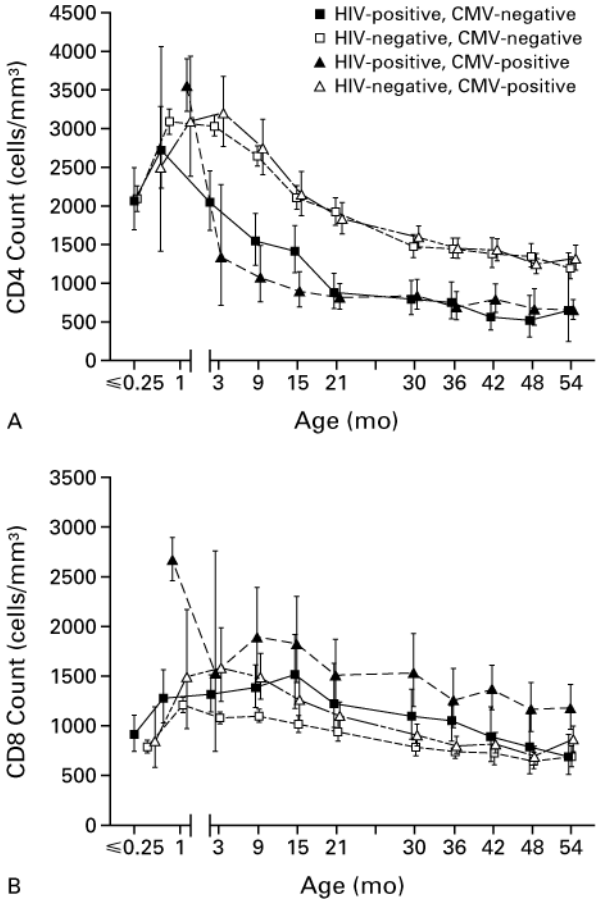

Figure 3.

Longitudinal Changes in Mean CD4 Counts (Panel A) and CD8 Counts (Panel B) According to HIV-1 Status, Age, and CMV Status (as a Time-Dependent Covariate).

Children were classified according to CMV status at the time of each lymphocyte measurement. The trend lines represent the model-based means, with 95 percent confidence intervals. Children infected with both HIV-1 and CMV had lower mean CD4 counts at 15 months of age (P=0.008) than those infected only with HIV-1 (Panel A). Coinfected children had significantly higher mean CD8 counts at 1, 9, 30, 42, and 54 months of age (P<0.001, P=0.03, P=0.04, P=0.008, and P=0.002, respectively) than those infected only with HIV-1 (Panel B). Among the HIV-1–uninfected children, those with CMV infection had significantly higher mean CD8 counts at 3, 9, 15, 21, and 54 months of age (P=0.003, P<0.001, P=0.03, P=0.05, and P=0.04, respectively) than those without CMV infection.

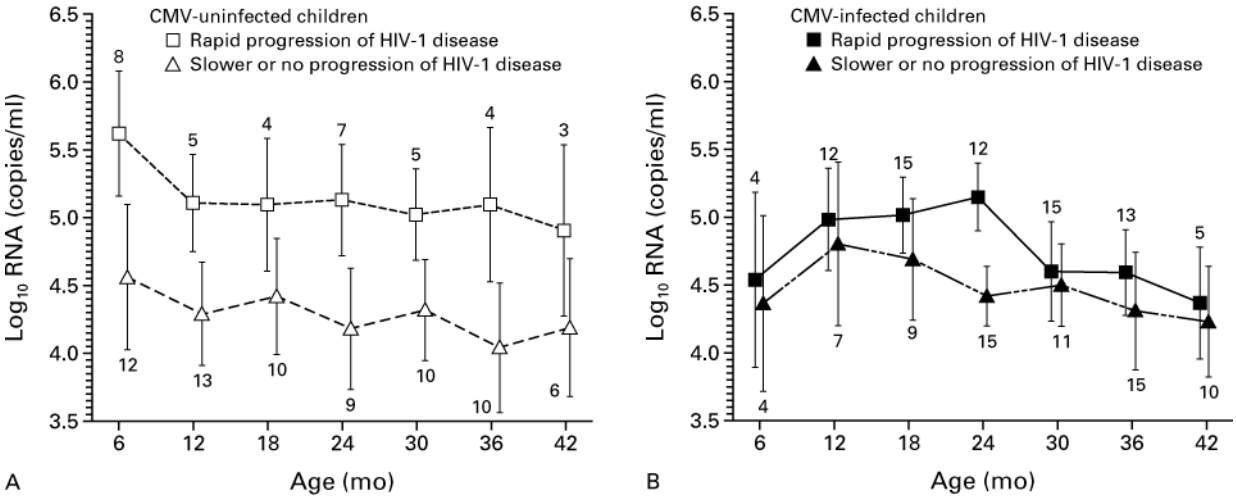

Figure 4.

Longitudinal Changes in Mean HIV-1 RNA Levels According to HIV-1 Disease-Progression Status, Age, and CMV Status (as a Time-Dependent Covariate).

Children were classified according to CMV status at the time of each HIV-1 RNA measurement. The trend lines represent the modelbased means and 95 percent confidence intervals. Among CMV-uninfected children (Panel A), those with rapid progression of HIV-1 disease (29 children) had significantly higher mean levels of HIV-1 RNA than those with slower or no progression (37 children) at all ages (P=0.004, P=0.002, P=0.04, P=0.002, P=0.007, P=0.006, and P=0.08 at ages 6, 12, 18, 24, 30, 36, and 42 months, respectively). Among CMV-infected children (Panel B), there were no significant differences in HIV-1 RNA levels between those with rapid progression and those with slower or no progression of disease, except for children 24 months of age (P<0.001). Numbers above and below the bars indicate numbers of children.

Table 1

CDC Class C Symptoms and Deaths in the First 18 Months of Life among HIV-1–Infected Children According to Their CMV Status.

Variable	CMV Status At 18 Mo	
	positive (n=40)	negative (n=23)
CDC class C symptom		
Wasting syndrome	2	1
Loss of developmental milestones or intellectual ability	8	2
Impaired brain growth	5	0
Progressive symmetric motor deficits	11	2
Pneumocystis carinii pneumonia	6	1
Candidiasis (esophageal, tracheal, bronchial, or pulmonary)	5	0
Mycobacterial infection (noncutaneous, extrapulmonary, or disseminated)	3	0
CMV disease*	3	0
Two or more serious bacterial infections	2	0
Any of the above	20	5
Death	3†	0

*CMV disease consisted of one case of disseminated CMV disease, one case of CMV colitis, and one case of CMV of the lung.

†One infant did not have CDC class C symptoms, one had progressive symmetric motor deficits and disseminated CMV disease, and one had loss of developmental milestones or intellectual ability, impaired brain growth, progressive symmetric motor deficits, and candidiasis.